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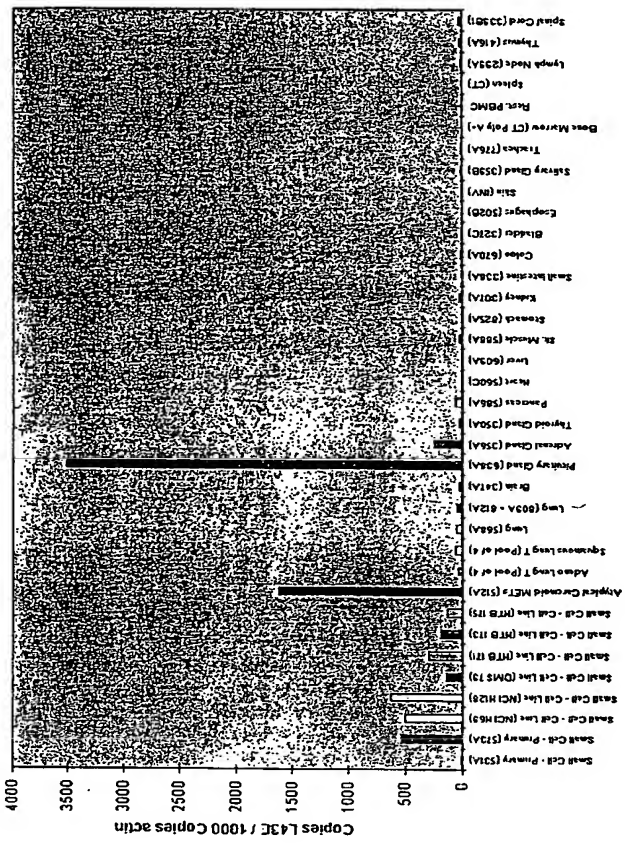

(57) Abstract: Compositions and methods for the therapy and diagnosis of cancer, particularly lung cancer, are disclosed. Illustrative compositions comprise one or more lung tumor polypeptides, immunogenic portions thereof, polynucleotides that encode such polypeptides, antigen presenting cell that expresses such polypeptides, and T cells that are specific for cells expressing such polypeptides. The disclosed compositions are useful, for example, in the diagnosis, prevention and/or treatment of diseases, particularly lung cancer.

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COMPOSITIONS AND METHODS FOR THE THERAPY AND DIAGNOSIS OF LUNG CANCER

TECHNICAL FIELD OF THE INVENTION

The present invention relates generally to therapy and diagnosis of cancer, such as lung cancer. the invention is more specifically related to polypeptides, comprising at least a portion of a lung tumor protein, and to polynucleotides encoding such polypeptides. such polypeptides and polynucleotides are useful in pharmaceutical compositions, *e.g.*, vaccines, and other compositions for the diagnosis and treatment of lung cancer.

BACKGROUND OF THE INVENTION

Lung cancer is the primary cause of cancer death among both men and women in the U.S., with an estimated 172,000 new cases being reported in 1994. The five-year survival rate among all lung cancer patients, regardless of the stage of disease at diagnosis, is only 13%. This contrasts with a five-year survival rate of 46% among cases detected while the disease is still localized. However, only 16% of lung cancers are discovered before the disease has spread.

Early detection is difficult since clinical symptoms are often not seen until the disease has reached an advanced stage. Currently, diagnosis is aided by the use of chest x-rays, analysis of the type of cells contained in sputum and fiberoptic examination of the bronchial passages. Treatment regimens are determined by the type and stage of the cancer, and include surgery, radiation therapy and/or chemotherapy. In spite of considerable research into therapies for the disease, lung cancer remains difficult to treat.

Accordingly, there remains a need in the art for improved vaccines, treatment methods and diagnostic techniques for lung cancer.

SUMMARY OF THE INVENTION

In one aspect, the present invention provides polynucleotide compositions comprising a sequence selected from the group consisting of:

(a) sequences provided in SEQ ID NO:1-232, 243-396, 398-412, 414-424 and 437-440;

(b) complements of the sequences provided in SEQ ID NO:1-232, 243-396, 398-412, 414-424 and 437-440;

(c) sequences consisting of at least 20 contiguous residues of a sequence provided in SEQ ID NO:1-232, 243-396, 398-412, 414-424 and 437-440;

(d) sequences that hybridize to a sequence provided in SEQ ID NO:1-232, 243-396, 398-412, 414-424 and 437-440, under moderately stringent conditions;

(e) sequences having at least 75% identity to a sequence of SEQ ID NO:1-232, 243-396, 398-412, 414-424 and 437-440;

(f) sequences having at least 90% identity to a sequence of SEQ ID NO:1-232, 243-396, 398-412, 414-424 and 437-440; and

(g) degenerate variants of a sequence provided in SEQ ID NO:1-232, 243-396, 398-412, 414-424 and 437-440.

In one preferred embodiment, the polynucleotide compositions of the invention are expressed in at least about 20%, more preferably in at least about 30%, and most preferably in at least about 50% of lung tumor samples tested, at a level that is at least about 2-fold, preferably at least about 5-fold, and most preferably at least about 10-fold higher than that for normal tissues.

The present invention, in another aspect, provides polypeptide compositions comprising an amino acid sequence that is encoded by a polynucleotide sequence described above. In certain specific embodiments, the present invention provides polypeptide compositions comprising an amino acid sequence selected from the group consisting of sequences recited in SEQ ID NO:229-232, 237-242, 397, 413 and 425-436.

In certain preferred embodiments, the polypeptides and/or polynucleotides of the present invention are immunogenic, *i.e.*, they are capable of eliciting an immune response, particularly a humoral and/or cellular immune response, as further described herein.

The present invention further provides fragments, variants and/or derivatives of the disclosed polypeptide and/or polynucleotide sequences, wherein the fragments, variants and/or derivatives preferably have a level of immunogenic activity of at least about 50%, preferably at least about 70% and more preferably at least about 90% of the level of immunogenic activity of a polypeptide sequence set forth in SEQ ID NOs: 229-232, 237-242, 397, 413 and 425-436, or a polypeptide sequence encoded by a polynucleotide sequence set forth in SEQ ID NOs: 1-232, 243-396, 398-412, 414-424 and 437-440.

The present invention further provides polynucleotides that encode a polypeptide described above, expression vectors comprising such polynucleotides and host cells transformed or transfected with such expression vectors.

Within other aspects, the present invention provides pharmaceutical compositions comprising a polypeptide or polynucleotide as described above and a physiologically acceptable carrier.

Within a related aspect of the present invention, the pharmaceutical compositions, *e.g.*, vaccine compositions, are provided for prophylactic or therapeutic applications. Such compositions generally comprise an immunogenic polypeptide or polynucleotide of the invention and an immunostimulant, such as an adjuvant.

The present invention further provides pharmaceutical compositions that comprise: (a) an antibody or antigen-binding fragment thereof that specifically binds to a polypeptide of the present invention, or a fragment thereof; and (b) a physiologically acceptable carrier.

Within further aspects, the present invention provides pharmaceutical compositions comprising: (a) an antigen presenting cell that expresses a polypeptide as described above and (b) a pharmaceutically acceptable carrier or excipient. Illustrative antigen presenting cells include dendritic cells, macrophages, monocytes, fibroblasts and B cells.

Within related aspects, pharmaceutical compositions are provided that comprise: (a) an antigen presenting cell that expresses a polypeptide as described above and (b) an immunostimulant.

The present invention further provides, in other aspects, fusion proteins that comprise at least one polypeptide as described above, as well as polynucleotides

encoding such fusion proteins, typically in the form of pharmaceutical compositions, *e.g.*, vaccine compositions, comprising a physiologically acceptable carrier and/or an immunostimulant. The fusions proteins may comprise multiple immunogenic polypeptides or portions/variants thereof, as described herein, and may further comprise one or more polypeptide segments for facilitating the expression, purification and/or immunogenicity of the polypeptide(s).

Within further aspects, the present invention provides methods for stimulating an immune response in a patient, preferably a T cell response in a human patient, comprising administering a pharmaceutical composition described herein. The patient may be afflicted with lung cancer, in which case the methods provide treatment for the disease, or patient considered at risk for such a disease may be treated prophylactically.

Within further aspects, the present invention provides methods for inhibiting the development of a cancer in a patient, comprising administering to a patient a pharmaceutical composition as recited above. The patient may be afflicted with lung cancer, in which case the methods provide treatment for the disease, or patient considered at risk for such a disease may be treated prophylactically.

The present invention further provides, within other aspects, methods for removing tumor cells from a biological sample, comprising contacting a biological sample with T cells that specifically react with a polypeptide of the present invention, wherein the step of contacting is performed under conditions and for a time sufficient to permit the removal of cells expressing the protein from the sample.

Within related aspects, methods are provided for inhibiting the development of a cancer in a patient, comprising administering to a patient a biological sample treated as described above.

Methods are further provided, within other aspects, for stimulating and/or expanding T cells specific for a polypeptide of the present invention, comprising contacting T cells with one or more of: (i) a polypeptide as described above; (ii) a polynucleotide encoding such a polypeptide; and/or (iii) an antigen presenting cell that expresses such a polypeptide; under conditions and for a time sufficient to permit the stimulation and/or expansion of T cells. Isolated T cell populations comprising T cells prepared as described above are also provided.

Within further aspects, the present invention provides methods for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of a T cell population as described above.

The present invention further provides methods for inhibiting the development of a cancer in a patient, comprising the steps of: (a) incubating $CD4^+$ and/or $CD8^+$ T cells isolated from a patient with one or more of: (i) a polypeptide comprising at least an immunogenic portion of polypeptide disclosed herein; (ii) a polynucleotide encoding such a polypeptide; and (iii) an antigen-presenting cell that expressed such a polypeptide; and (b) administering to the patient an effective amount of the proliferated T cells, and thereby inhibiting the development of a cancer in the patient. Proliferated cells may, but need not, be cloned prior to administration to the patient.

Within further aspects, the present invention provides methods for determining the presence or absence of a cancer, preferably a lung cancer, in a patient comprising: (a) contacting a biological sample obtained from a patient with a binding agent that binds to a polypeptide as recited above; (b) detecting in the sample an amount of polypeptide that binds to the binding agent; and (c) comparing the amount of polypeptide with a predetermined cut-off value, and therefrom determining the presence or absence of a cancer in the patient. Within preferred embodiments, the binding agent is an antibody, more preferably a monoclonal antibody.

The present invention also provides, within other aspects, methods for monitoring the progression of a cancer in a patient. Such methods comprise the steps of: (a) contacting a biological sample obtained from a patient at a first point in time with a binding agent that binds to a polypeptide as recited above; (b) detecting in the sample an amount of polypeptide that binds to the binding agent; (c) repeating steps (a) and (b) using a biological sample obtained from the patient at a subsequent point in time; and (d) comparing the amount of polypeptide detected in step (c) with the amount detected in step (b) and therefrom monitoring the progression of the cancer in the patient.

The present invention further provides, within other aspects, methods for determining the presence or absence of a cancer in a patient, comprising the steps of: (a) contacting a biological sample obtained from a patient with an oligonucleotide that

hybridizes to a polynucleotide that encodes a polypeptide of the present invention; (b) detecting in the sample a level of a polynucleotide, preferably mRNA, that hybridizes to the oligonucleotide; and (c) comparing the level of polynucleotide that hybridizes to the oligonucleotide with a predetermined cut-off value, and therefrom determining the presence or absence of a cancer in the patient. Within certain embodiments, the amount of mRNA is detected via polymerase chain reaction using, for example, at least one oligonucleotide primer that hybridizes to a polynucleotide encoding a polypeptide as recited above, or a complement of such a polynucleotide. Within other embodiments, the amount of mRNA is detected using a hybridization technique, employing an oligonucleotide probe that hybridizes to a polynucleotide that encodes a polypeptide as recited above, or a complement of such a polynucleotide.

In related aspects, methods are provided for monitoring the progression of a cancer in a patient, comprising the steps of: (a) contacting a biological sample obtained from a patient with an oligonucleotide that hybridizes to a polynucleotide that encodes a polypeptide of the present invention; (b) detecting in the sample an amount of a polynucleotide that hybridizes to the oligonucleotide; (c) repeating steps (a) and (b) using a biological sample obtained from the patient at a subsequent point in time; and (d) comparing the amount of polynucleotide detected in step (c) with the amount detected in step (b) and therefrom monitoring the progression of the cancer in the patient.

Within further aspects, the present invention provides antibodies, such as monoclonal antibodies, that bind to a polypeptide as described above, as well as diagnostic kits comprising such antibodies. Diagnostic kits comprising one or more oligonucleotide probes or primers as described above are also provided.

These and other aspects of the present invention will become apparent upon reference to the following detailed description and attached drawings. All references disclosed herein are hereby incorporated by reference in their entirety as if each was incorporated individually.

BRIEF DESCRIPTION OF THE DRAWINGS AND SEQUENCE IDENTIFIERS

Figure 1 is a bar graph showing expression of clone SCC2-51 in normal tissues and tumor tissues.

SEQ ID NO:1 is the determined cDNA sequence for LSC-1.

SEQ ID NO:2 is the determined cDNA sequence for LSC-2.

SEQ ID NO:3 is the determined cDNA sequence for LSC-3.

SEQ ID NO:4 is the determined cDNA sequence for LSC-5.

SEQ ID NO:5 is the determined cDNA sequence for LSC-6.

SEQ ID NO:6 is the determined cDNA sequence for LSC-7.

SEQ ID NO:7 is the determined cDNA sequence for LSC-9.

SEQ ID NO:8 is the determined cDNA sequence for LSC-10.

SEQ ID NO:9 is the determined cDNA sequence for LSC-11.

SEQ ID NO:10 is the determined cDNA sequence for LSC-13.

SEQ ID NO:11 is the determined cDNA sequence for LSC-15.

SEQ ID NO:12 is the determined cDNA sequence for LSC-20.

SEQ ID NO:13 is the determined cDNA sequence for LSC-23.

SEQ ID NO:14 is the determined cDNA sequence for LSC-24.

SEQ ID NO:15 is the determined cDNA sequence for LSC-25.

SEQ ID NO:16 is the determined cDNA sequence for LSC-26.

SEQ ID NO:17 is the determined cDNA sequence for LSC-27.

SEQ ID NO:18 is the determined cDNA sequence for LSC-28.

SEQ ID NO:19 is the determined cDNA sequence for LSC-29.

SEQ ID NO:20 is the determined cDNA sequence for LSC-30.

SEQ ID NO:21 is the determined cDNA sequence for LSC-31.

SEQ ID NO:22 is the determined cDNA sequence for LSC-33.

SEQ ID NO:23 is the determined cDNA sequence for LSC-34.

SEQ ID NO:24 is the determined cDNA sequence for LSC-35.

SEQ ID NO:25 is the determined cDNA sequence for LSC-37.

SEQ ID NO:26 is the determined cDNA sequence for LSC-39.

SEQ ID NO:27 is the determined cDNA sequence for LSC-43.

SEQ ID NO:28 is the determined cDNA sequence for LSC-46.

SEQ ID NO:29 is the determined cDNA sequence for LSC-49.

SEQ ID NO:30 is the determined cDNA sequence for LSC-51.

SEQ ID NO:31 is the determined cDNA sequence for LSC-53.

SEQ ID NO:32 is the determined cDNA sequence for LSC-55.

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SEQ ID NO:41 is the determined cDNA sequence for LSC-77.
SEQ ID NO:42 is the determined cDNA sequence for LSC-78.
SEQ ID NO:43 is the determined cDNA sequence for LSC-81.
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SEQ ID NO:45 is the determined cDNA sequence for LSC-101.
SEQ ID NO:46 is the determined cDNA sequence for LSC-102.
SEQ ID NO:47 is the determined cDNA sequence for LSC-103.
SEQ ID NO:48 is the determined cDNA sequence for LSC-105.
SEQ ID NO:49 is the determined cDNA sequence for LSC-110.
SEQ ID NO:50 is the determined cDNA sequence for LSC-125.
SEQ ID NO:51 is the determined cDNA sequence for LSC-134.
SEQ ID NO:52 is the determined cDNA sequence for LSC-142.
SEQ ID NO:53 is the determined cDNA sequence for LSC-144.
SEQ ID NO:54 is the determined cDNA sequence for LSC-148.
SEQ ID NO:55 is the determined cDNA sequence for LSC-149.
SEQ ID NO:56 is the determined cDNA sequence for LSC-153.
SEQ ID NO:57 is the determined cDNA sequence for LSC-163.
SEQ ID NO:58 is the determined cDNA sequence for LSC-170.
SEQ ID NO:59 is the determined cDNA sequence for LSC-171.
SEQ ID NO:60 is the determined cDNA sequence for LSC-172.
SEQ ID NO:61 is the determined cDNA sequence for LSC-175.
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SEQ ID NO:75 is the determined cDNA sequence for LSC-215.
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SEQ ID NO:226 is the determined cDNA sequence for clone SCC2-266.

SEQ ID NO:227 is the determined cDNA sequence for clone SCC2-275.

SEQ ID NO:228 is the determined cDNA sequence for clone SCC2-283.

SEQ ID NO:229 is the determined cDNA extended sequence for clone SCC2-5, which relates to SEQ ID NO:146.

SEQ ID NO:230 is the determined cDNA extended sequence for clone SCC2-14, which relates to SEQ ID NO:153.

SEQ ID NO:231 is the determined cDNA sequence for clone SCC2-50.

SEQ ID NO:232 is the determined cDNA extended sequence for clone SCC2-51, which relates to SEQ ID NO:175.

SEQ ID NO:233 is the amino acid sequence encoded by SEQ ID NO:229.

SEQ ID NO:234 is the amino acid sequence encoded by SEQ ID NO:230.

SEQ ID NO:235 is the amino acid sequence encoded by SEQ ID NO:231.

SEQ ID NO:236 is the amino acid sequence encoded by SEQ ID NO:232.

SEQ ID NO:237 is GenBank Accession No. CAA58926

SEQ ID NO:238 is GenBank Accession No. BAA91327

SEQ ID NO:239 is GenBank Accession No. BAA22955

SEQ ID NO:240 is GenBank Accession No. NP_004258

SEQ ID NO:241 is GenBank Accession No. AAF61208

SEQ ID NO:242 is GenBank Accession No. CAA26370

SEQ ID NO:243 is the determined cDNA sequence for '56908.1

SEQ ID NO:244 is the determined cDNA sequence for '56909.1

SEQ ID NO:245 is the determined cDNA sequence for '56911.1

SEQ ID NO:246 is GenBank Accession No. AK000700

SEQ ID NO:247 is the determined cDNA sequence for '56912.1

SEQ ID NO:248 is GenBank Accession No. AB006624

SEQ ID NO:249 is the determined cDNA sequence for '56913.1

SEQ ID NO:250 is GenBank Accession No. NM_004267
SEQ ID NO:251 is the determined cDNA sequence for '56916.1
SEQ ID NO:252 is the determined cDNA sequence for '56917.1
SEQ ID NO:253 is the determined cDNA sequence for '56921.1
SEQ ID NO:254 is GenBank Accession No. AF216751
SEQ ID NO:255 is the determined cDNA sequence for '56922.1
SEQ ID NO:256 is GenBank Accession No. X02530
SEQ ID NO:257 is the determined cDNA sequence for '56923.1
SEQ ID NO:258 is the determined cDNA sequence for 54533.1
SEQ ID NO:259 is the determined cDNA sequence for 54534.1
SEQ ID NO:260 is the determined cDNA sequence for 54536.1
SEQ ID NO:261 is the determined cDNA sequence for 54538.1
SEQ ID NO:262 is the determined cDNA sequence for 54540.1
SEQ ID NO:263 is the determined cDNA sequence for 55084.1
SEQ ID NO:264 is the determined cDNA sequence for 55086.1
SEQ ID NO:265 is the determined cDNA sequence for 54555.1
SEQ ID NO:266 is the determined cDNA sequence for 54557.1
SEQ ID NO:267 is the determined cDNA sequence for 54564.1
SEQ ID NO:268 is the determined cDNA sequence for 55098.1
SEQ ID NO:269 is the determined cDNA sequence for 55473.1
SEQ ID NO:270 is the determined cDNA sequence for 55104.1
SEQ ID NO:271 is the determined cDNA sequence for 55105.1
SEQ ID NO:272 is the determined cDNA sequence for 55107.1
SEQ ID NO:273 is the determined cDNA sequence for 55108.1
SEQ ID NO:274 is the determined cDNA sequence for 55114.1
SEQ ID NO:275 is the determined cDNA sequence for 55477.1
SEQ ID NO:276 is the determined cDNA sequence for 55482.1
SEQ ID NO:277 is the determined cDNA sequence for 55483.1
SEQ ID NO:278 is the determined cDNA sequence for 55485.1
SEQ ID NO:279 is the determined cDNA sequence for 55487.1
SEQ ID NO:280 is the determined cDNA sequence for 55488.1
SEQ ID NO:281 is the determined cDNA sequence for 55087.1

SEQ ID NO:282 is the determined cDNA sequence for 55089.1
SEQ ID NO:283 is the determined cDNA sequence for 55092.1
SEQ ID NO:284 is the determined cDNA sequence for 55093.1
SEQ ID NO:285 is the determined cDNA sequence for 56926.1
SEQ ID NO:286 is the determined cDNA sequence for 56930.1
SEQ ID NO:287 is the determined cDNA sequence for 56944.1
SEQ ID NO:288 is the determined cDNA sequence for 56945.1
SEQ ID NO:289 is the determined cDNA sequence for 55490.1
SEQ ID NO:290 is the determined cDNA sequence for 55495.1
SEQ ID NO:291 is the determined cDNA sequence for 55504.1
SEQ ID NO:292 is the determined cDNA sequence for 55506.1
SEQ ID NO:293 is the determined cDNA sequence for 56480.1
SEQ ID NO:294 is the determined cDNA sequence for 56482.1
SEQ ID NO:295 is the determined cDNA sequence for 56484.1
SEQ ID NO:296 is the determined cDNA sequence for 56487.1
SEQ ID NO:297 is the determined cDNA sequence for 56488.1
SEQ ID NO:298 is the determined cDNA sequence for 56490.1
SEQ ID NO:299 is the determined cDNA sequence for 56493.1
SEQ ID NO:300 is the determined cDNA sequence for 56494.1
SEQ ID NO:301 is the determined cDNA sequence for 56495.1
SEQ ID NO:302 is the determined cDNA sequence for 56499.1
SEQ ID NO:303 is the determined cDNA sequence for 56517.1
SEQ ID NO:304 is the determined cDNA sequence for 56952.1
SEQ ID NO:305 is the determined cDNA sequence for 56953.1
SEQ ID NO:306 is the determined cDNA sequence for 56959.1
SEQ ID NO:307 is the determined cDNA sequence for 57139.1
SEQ ID NO:308 is the determined cDNA sequence for 57078.1
SEQ ID NO:309 is the determined cDNA sequence for 57092.1
SEQ ID NO:310 is the determined cDNA sequence for 57099.1
SEQ ID NO:311 is the determined cDNA sequence for 57100.1
SEQ ID NO:312 is the determined cDNA sequence for 57105.1
SEQ ID NO:313 is the determined cDNA sequence for 57111.1

SEQ ID NO:314 is the determined cDNA sequence for 57117.1
SEQ ID NO:315 is the determined cDNA sequence for 57121.1
SEQ ID NO:316 is the determined cDNA sequence for 57124.1
SEQ ID NO:317 is the determined cDNA sequence for 57125.1
SEQ ID NO:318 is the determined cDNA sequence for 54800.2
SEQ ID NO:319 is the determined cDNA sequence for 54802.2
SEQ ID NO:320 is the determined cDNA sequence for 54803.2
SEQ ID NO:321 is the determined cDNA sequence for 54805.2
SEQ ID NO:322 is the determined cDNA sequence for 54806.2
SEQ ID NO:323 is the determined cDNA sequence for 54809.2
SEQ ID NO:324 is the determined cDNA sequence for 54810.2
SEQ ID NO:325 is the determined cDNA sequence for 54813.2
SEQ ID NO:326 is the determined cDNA sequence for 54814.2
SEQ ID NO:327 is the determined cDNA sequence for 54816.2
SEQ ID NO:328 is the determined cDNA sequence for 54817.2
SEQ ID NO:329 is the determined cDNA sequence for 54819.2
SEQ ID NO:330 is the determined cDNA sequence for 54821.2
SEQ ID NO:331 is the determined cDNA sequence for 54823.2
SEQ ID NO:332 is the determined cDNA sequence for 54824.2
SEQ ID NO:333 is the determined cDNA sequence for 54825.2
SEQ ID NO:334 is the determined cDNA sequence for 54826.2
SEQ ID NO:335 is the determined cDNA sequence for 54827.2
SEQ ID NO:336 is the determined cDNA sequence for 54829.2
SEQ ID NO:337 is the determined cDNA sequence for 54830.2
SEQ ID NO:338 is the determined cDNA sequence for 54832.2
SEQ ID NO:339 is the determined cDNA sequence for 55800.2
SEQ ID NO:340 is the determined cDNA sequence for 55801.2
SEQ ID NO:341 is the determined cDNA sequence for 55803.2
SEQ ID NO:342 is the determined cDNA sequence for 55804.2
SEQ ID NO:343 is the determined cDNA sequence for 55805.2
SEQ ID NO:344 is the determined cDNA sequence for 55806.2
SEQ ID NO:345 is the determined cDNA sequence for 55808.2

SEQ ID NO:346 is the determined cDNA sequence for 55810.2

SEQ ID NO:347 is the determined cDNA sequence for 55811.2

SEQ ID NO:348 is the determined cDNA sequence for 55812.2

SEQ ID NO:349 is the determined cDNA sequence for 55814.2

SEQ ID NO:350 is the determined cDNA sequence for 55816.2

SEQ ID NO:351 is the determined cDNA sequence for 55817.2

SEQ ID NO:352 is the determined cDNA sequence for 55819.2

SEQ ID NO:353 is the determined cDNA sequence for 55820.2

SEQ ID NO:354 is the determined cDNA sequence for 55823.2

SEQ ID NO:355 is the determined cDNA sequence for 55824.2

SEQ ID NO:356 is the determined cDNA sequence for 55826.2

SEQ ID NO:357 is the determined cDNA sequence for 55828.2

SEQ ID NO:358 is the determined cDNA sequence for 55829.2

SEQ ID NO:359 is the determined cDNA sequence for 55831.2

SEQ ID NO:360 is the determined cDNA sequence for 55832.2

SEQ ID NO:361 is the determined cDNA sequence for 55833.2

SEQ ID NO:362 is the determined cDNA sequence for 55834.2

SEQ ID NO:363 is the determined cDNA sequence for 55835.2

SEQ ID NO:364 is the determined cDNA sequence for 55838.2

SEQ ID NO:365 is a predicted extended cDNA sequence for clone 48137 (L578S) having the isolated sequence of SEQ ID NO:89)

SEQ ID NO:366 is the predicted amino acid encoded by SEQ ID NO:365

SEQ ID NO:367 is the determined cDNA sequence for 49949.5

SEQ ID NO:368 is the determined cDNA sequence for 49952.1

SEQ ID NO:369 is the determined cDNA sequence for 49956;contig 29

SEQ ID NO:370 is the determined cDNA sequence for 49960.4

SEQ ID NO:371 is the determined cDNA sequence for 49961;contig 21

SEQ ID NO:372 is the determined cDNA sequence for 49962.4

SEQ ID NO:373 is the determined cDNA sequence for 49962.5

SEQ ID NO:374 is the determined cDNA sequence for 49965.1

SEQ ID NO:375 is the determined cDNA sequence for 49966.1

SEQ ID NO:376 is the determined cDNA sequence for 49971.1

SEQ ID NO:377 is the determined cDNA sequence for 49975.1

SEQ ID NO:378 is the determined cDNA sequence for 49982.1

SEQ ID NO:379 is the determined cDNA sequence for 49986.1

SEQ ID NO:380 is the determined cDNA sequence for 49988.1

SEQ ID NO:381 is the determined cDNA sequence for 49993.1

SEQ ID NO:382 is the determined cDNA sequence for 49995.1

SEQ ID NO:383 is the determined cDNA sequence for 49996;contig 22

SEQ ID NO:384 is the determined cDNA sequence for 49999.1

SEQ ID NO:385 is the determined cDNA sequence for 50006;contig 23

SEQ ID NO:386 is the determined cDNA sequence for 50007.1

SEQ ID NO:387 is the determined cDNA sequence for 50009.3

SEQ ID NO:388 is the determined cDNA sequence for 50014.1

SEQ ID NO:389 is the determined cDNA sequence for 50016;contig 24

SEQ ID NO:390 is the determined cDNA sequence for 50017.1

SEQ ID NO:391 is the determined cDNA sequence for 50019.1

SEQ ID NO:392 is the determined cDNA sequence for 50022.1

SEQ ID NO:393 is the determined cDNA sequence for 50023.1

SEQ ID NO:394 is the determined cDNA sequence for 50024.1

SEQ ID NO:395 is the determined cDNA sequence for 50033.1

SEQ ID NO:396 is an extended cDNA sequence for SCC2-54 (SEQ ID NO:178)

SEQ ID NO:397 is the amino acid sequence encoded by SEQ ID NO:396

SEQ ID NO:398 is the determined cDNA sequence for 56908.1

SEQ ID NO:399 is the determined cDNA sequence for 56911.1

SEQ ID NO:400 is the determined cDNA sequence for 56912.1

SEQ ID NO:401 is the determined cDNA sequence for 56913.1

SEQ ID NO:402 is the determined cDNA sequence for 56916.1

SEQ ID NO:403 is the determined cDNA sequence for 56917.1

SEQ ID NO:404 is the determined cDNA sequence for 56921.1

SEQ ID NO:405 is the determined cDNA sequence for 56922.1

SEQ ID NO:406 is the determined cDNA sequence for 56923.1

SEQ ID NO:407 is the determined cDNA sequence for 60974.1

SEQ ID NO:408 is the determined cDNA sequence for 60976.1

SEQ ID NO:409 is the determined cDNA sequence for 60977.1

SEQ ID NO:410 is the determined cDNA sequence for 60978.1

SEQ ID NO:411 is the determined cDNA sequence for 60980.1

SEQ ID NO:412 is an extended cDNA sequence for LSC-49 (SEQ ID NO:29)

SEQ ID NO:413 is the amino acid sequence encoded by SEQ ID NO:412

SEQ ID NO:414 is an extended cDNA sequence for LSC-39 (SEQ ID NO:26)

SEQ ID NO:415 is an extended cDNA sequence for LSC-46 (SEQ ID NO:28)

SEQ ID NO:416 is an extended cDNA sequence for LSC-49 (SEQ ID NO:29)

SEQ ID NO:417 is an extended cDNA sequence for LSC-51 (SEQ ID NO:30)

SEQ ID NO:418 is an extended cDNA sequence for LSC-55 (SEQ ID NO:32)

SEQ ID NO:419 is an extended cDNA sequence for LSC-64 (SEQ ID NO:35)

SEQ ID NO:420 is an extended cDNA sequence for LSC-78 (SEQ ID NO:42)

SEQ ID NO:421 is an extended cDNA sequence for LSC-103 (SEQ ID NO:47)

SEQ ID NO:422 is an extended cDNA sequence for LSC-144 (SEQ ID NO:53)

SEQ ID NO:423 is an extended cDNA sequence for LSC-148 (SEQ ID NO:54)

SEQ ID NO:424 is an extended cDNA sequence for LSC-210 (SEQ ID NO:74)

SEQ ID NO:425 is the amino acid sequence encoded by SEQ ID NO:414

SEQ ID NO:426 is the amino acid sequence encoded by SEQ ID NO:415

SEQ ID NO:427 is the amino acid sequence encoded by SEQ ID NO:416

SEQ ID NO:428 is the amino acid sequence encoded by SEQ ID NO:417

SEQ ID NO:429 is the amino acid sequence encoded by SEQ ID NO:418

SEQ ID NO:430 is the amino acid sequence encoded by SEQ ID NO:419

SEQ ID NO:431 is the amino acid sequence encoded by SEQ ID NO:420

SEQ ID NO:432 is the amino acid sequence encoded by SEQ ID NO:421

SEQ ID NO:433 is the amino acid sequence encoded by SEQ ID NO:422

SEQ ID NO:434 is the amino acid sequence encoded by SEQ ID NO:423

SEQ ID NO:435 is the amino acid sequence encoded by SEQ ID NO:424

SEQ ID NO:436 is the amino acid sequence encoded by a second open reading frame (ORF-2) of clone SCC2-51, SEQ ID NO:175

SEQ ID NO:437 is the determined cDNA sequence for SCC2-16.

SEQ ID NO:438 is the determined cDNA sequence for SCC2-28.

SEQ ID NO:439 is the determined cDNA sequence for SCC2-62.

SEQ ID NO:440 is the determined cDNA sequence for SCC3-90.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed generally to compositions and their use in the therapy and diagnosis of cancer, particularly lung cancer. As described further below, illustrative compositions of the present invention include, but are not restricted to, polypeptides, particularly immunogenic polypeptides, polynucleotides encoding such polypeptides, antibodies and other binding agents, antigen presenting cells (APCs) and immune system cells (*e.g.*, T cells).

The practice of the present invention will employ, unless indicated specifically to the contrary, conventional methods of virology, immunology, microbiology, molecular biology and recombinant DNA techniques within the skill of the art, many of which are described below for the purpose of illustration. Such techniques are explained fully in the literature. See, *e.g.*, Sambrook, et al. Molecular Cloning: A Laboratory Manual (2nd Edition, 1989); Maniatis et al. Molecular Cloning:

A Laboratory Manual (1982); DNA Cloning: A Practical Approach, vol. I & II (D. Glover, ed.); Oligonucleotide Synthesis (N. Gait, ed., 1984); Nucleic Acid Hybridization (B. Hames & S. Higgins, eds., 1985); Transcription and Translation (B. Hames & S. Higgins, eds., 1984); Animal Cell Culture (R. Freshney, ed., 1986); Perbal, A Practical Guide to Molecular Cloning (1984).

All publications, patents and patent applications cited herein, whether supra or infra, are hereby incorporated by reference in their entirety.

As used in this specification and the appended claims, the singular forms "a," "an" and "the" include plural references unless the content clearly dictates otherwise.

Polypeptide Compositions

As used herein, the term "polypeptide" " is used in its conventional meaning, *i.e.*, as a sequence of amino acids. The polypeptides are not limited to a specific length of the product; thus, peptides, oligopeptides, and proteins are included within the definition of polypeptide, and such terms may be used interchangeably herein unless specifically indicated otherwise. This term also does not refer to or exclude post-expression modifications of the polypeptide, for example, glycosylations, acetylations, phosphorylations and the like, as well as other modifications known in the art, both naturally occurring and non-naturally occurring. A polypeptide may be an entire protein, or a subsequence thereof. Particular polypeptides of interest in the context of this invention are amino acid subsequences comprising epitopes, *i.*e., antigenic determinants substantially responsible for the immunogenic properties of a polypeptide and being capable of evoking an immune response.

Particularly illustrative polypeptides of the present invention comprise those encoded by a polynucleotide sequence set forth in any one of SEQ ID NOs: 1-232, 243-396, 398-412, 414-424 and 437-440, or a sequence that hybridizes under moderately stringent conditions, or, alternatively, under highly stringent conditions, to a polynucleotide sequence set forth in any one of SEQ ID NOs: 1-232, 243-396, 398-412, 414-424 and 437-440. Certain illustrative polypeptides of the invention comprise amino acid sequences as set forth in any one of SEQ ID NOs: 229-232, 237-242, 397, 413 and 425-436.

The polypeptides of the present invention are sometimes herein referred to as lung tumor proteins or lung tumor polypeptides, as an indication that their identification has been based at least in part upon their increased levels of expression in lung tumor samples. Thus, a "lung tumor polypeptide" or "lung tumor protein," refers generally to a polypeptide sequence of the present invention, or a polynucleotide sequence encoding such a polypeptide, that is expressed in a substantial proportion of lung tumor samples, for example preferably greater than about 20%, more preferably greater than about 30%, and most preferably greater than about 50% or more of lung tumor samples tested, at a level that is at least two fold, and preferably at least five fold, greater than the level of expression in normal tissues, as determined using a representative assay provided herein. A lung tumor polypeptide sequence of the invention, based upon its increased level of expression in tumor cells, has particular utility both as a diagnostic marker as well as a therapeutic target, as further described below.

In certain preferred embodiments, the polypeptides of the invention are immunogenic, *i.e.*, they react detectably within an immunoassay (such as an ELISA or T-cell stimulation assay) with antisera and/or T-cells from a patient with lung cancer. Screening for immunogenic activity can be performed using techniques well known to the skilled artisan. For example, such screens can be performed using methods such as those described in Harlow and Lane, *Antibodies: A Laboratory Manual,* Cold Spring Harbor Laboratory, 1988. In one illustrative example, a polypeptide may be immobilized on a solid support and contacted with patient sera to allow binding of antibodies within the sera to the immobilized polypeptide. Unbound sera may then be removed and bound antibodies detected using, for example, ^{125}I-labeled Protein A.

As would be recognized by the skilled artisan, immunogenic portions of the polypeptides disclosed herein are also encompassed by the present invention. An "immunogenic portion," as used herein, is a fragment of an immunogenic polypeptide of the invention that itself is immunologically reactive (*i.e.,* specifically binds) with the B-cells and/or T-cell surface antigen receptors that recognize the polypeptide. Immunogenic portions may generally be identified using well known techniques, such as those summarized in Paul, *Fundamental Immunology*, 3rd ed., 243-247 (Raven Press, 1993) and references cited therein. Such techniques include screening polypeptides for

the ability to react with antigen-specific antibodies, antisera and/or T-cell lines or clones. As used herein, antisera and antibodies are "antigen-specific" if they specifically bind to an antigen (*i.e.*, they react with the protein in an ELISA or other immunoassay, and do not react detectably with unrelated proteins). Such antisera and antibodies may be prepared as described herein, and using well-known techniques.

In one preferred embodiment, an immunogenic portion of a polypeptide of the present invention is a portion that reacts with antisera and/or T-cells at a level that is not substantially less than the reactivity of the full-length polypeptide (*e.g.*, in an ELISA and/or T-cell reactivity assay). Preferably, the level of immunogenic activity of the immunogenic portion is at least about 50%, preferably at least about 70% and most preferably greater than about 90% of the immunogenicity for the full-length polypeptide. In some instances, preferred immunogenic portions will be identified that have a level of immunogenic activity greater than that of the corresponding full-length polypeptide, *e.g.*, having greater than about 100% or 150% or more immunogenic activity.

In certain other embodiments, illustrative immunogenic portions may include peptides in which an N-terminal leader sequence and/or transmembrane domain have been deleted. Other illustrative immunogenic portions will contain a small N- and/or C-terminal deletion (*e.g.*, 1-30 amino acids, preferably 5-15 amino acids), relative to the mature protein.

In another embodiment, a polypeptide composition of the invention may also comprise one or more polypeptides that are immunologically reactive with T cells and/or antibodies generated against a polypeptide of the invention, particularly a polypeptide having an amino acid sequence disclosed herein, or to an immunogenic fragment or variant thereof.

In another embodiment of the invention, polypeptides are provided that comprise one or more polypeptides that are capable of eliciting T cells and/or antibodies that are immunologically reactive with one or more polypeptides described herein, or one or more polypeptides encoded by contiguous nucleic acid sequences contained in the polynucleotide sequences disclosed herein, or immunogenic fragments or variants thereof, or to one or more nucleic acid sequences which hybridize to one or more of these sequences under conditions of moderate to high stringency.

The present invention, in another aspect, provides polypeptide fragments comprising at least about 5, 10, 15, 20, 25, 50, or 100 contiguous amino acids, or more, including all intermediate lengths, of a polypeptide compositions set forth herein, such as those set forth in SEQ ID NOs: 229-232, 237-242, 397, 413 and 425-436, or those encoded by a polynucleotide sequence set forth in a sequence of SEQ ID NOs: 1-232, 243-396, 398-412, 414-424 and 437-440.

In another aspect, the present invention provides variants of the polypeptide compositions described herein. Polypeptide variants generally encompassed by the present invention will typically exhibit at least about 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% or more identity (determined as described below), along its length, to a polypeptide sequences set forth herein.

In one preferred embodiment, the polypeptide fragments and variants provide by the present invention are immunologically reactive with an antibody and/or T-cell that reacts with a full-length polypeptide specifically set for the herein.

In another preferred embodiment, the polypeptide fragments and variants provided by the present invention exhibit a level of immunogenic activity of at least about 50%, preferably at least about 70%, and most preferably at least about 90% or more of that exhibited by a full-length polypeptide sequence specifically set forth herein.

A polypeptide "variant," as the term is used herein, is a polypeptide that typically differs from a polypeptide specifically disclosed herein in one or more substitutions, deletions, additions and/or insertions. Such variants may be naturally occurring or may be synthetically generated, for example, by modifying one or more of the above polypeptide sequences of the invention and evaluating their immunogenic activity as described herein and/or using any of a number of techniques well known in the art.

For example, certain illustrative variants of the polypeptides of the invention include those in which one or more portions, such as an N-terminal leader sequence or transmembrane domain, have been removed. Other illustrative variants include variants in which a small portion (*e.g.*, 1-30 amino acids, preferably 5-15 amino acids) has been removed from the N- and/or C-terminal of the mature protein.

In many instances, a variant will contain conservative substitutions. A "conservative substitution" is one in which an amino acid is substituted for another amino acid that has similar properties, such that one skilled in the art of peptide chemistry would expect the secondary structure and hydropathic nature of the polypeptide to be substantially unchanged. As described above, modifications may be made in the structure of the polynucleotides and polypeptides of the present invention and still obtain a functional molecule that encodes a variant or derivative polypeptide with desirable characteristics, *e.g.*, with immunogenic characteristics. When it is desired to alter the amino acid sequence of a polypeptide to create an equivalent, or even an improved, immunogenic variant or portion of a polypeptide of the invention, one skilled in the art will typically change one or more of the codons of the encoding DNA sequence according to Table 1.

For example, certain amino acids may be substituted for other amino acids in a protein structure without appreciable loss of interactive binding capacity with structures such as, for example, antigen-binding regions of antibodies or binding sites on substrate molecules. Since it is the interactive capacity and nature of a protein that defines that protein's biological functional activity, certain amino acid sequence substitutions can be made in a protein sequence, and, of course, its underlying DNA coding sequence, and nevertheless obtain a protein with like properties. It is thus contemplated that various changes may be made in the peptide sequences of the disclosed compositions, or corresponding DNA sequences which encode said peptides without appreciable loss of their biological utility or activity.

TABLE 1

Amino Acids			Codons					
Alanine	Ala	A	GCA	GCC	GCG	GCU		
Cysteine	Cys	C	UGC	UGU				
Aspartic acid	Asp	D	GAC	GAU				
Glutamic acid	Glu	E	GAA	GAG				
Phenylalanine	Phe	F	UUC	UUU				
Glycine	Gly	G	GGA	GGC	GGG	GGU		
Histidine	His	H	CAC	CAU				
Isoleucine	Ile	I	AUA	AUC	AUU			
Lysine	Lys	K	AAA	AAG				
Leucine	Leu	L	UUA	UUG	CUA	CUC	CUG	CUU
Methionine	Met	M	AUG					
Asparagine	Asn	N	AAC	AAU				
Proline	Pro	P	CCA	CCC	CCG	CCU		
Glutamine	Gln	Q	CAA	CAG				
Arginine	Arg	R	AGA	AGG	CGA	CGC	CGG	CGU
Serine	Ser	S	AGC	AGU	UCA	UCC	UCG	UCU
Threonine	Thr	T	ACA	ACC	ACG	ACU		
Valine	Val	V	GUA	GUC	GUG	GUU		
Tryptophan	Trp	W	UGG					
Tyrosine	Tyr	Y	UAC	UAU				

In making such changes, the hydropathic index of amino acids may be considered. The importance of the hydropathic amino acid index in conferring interactive biologic function on a protein is generally understood in the art (Kyte and Doolittle, 1982, incorporated herein by reference). It is accepted that the relative hydropathic character of the amino acid contributes to the secondary structure of the resultant protein, which in turn defines the interaction of the protein with other molecules, for example, enzymes, substrates, receptors, DNA, antibodies, antigens, and the like. Each amino acid has been assigned a hydropathic index on the basis of its hydrophobicity and charge characteristics (Kyte and Doolittle, 1982). These values are:

isoleucine (+4.5); valine (+4.2); leucine (+3.8); phenylalanine (+2.8); cysteine/cystine (+2.5); methionine (+1.9); alanine (+1.8); glycine (–0.4); threonine (–0.7); serine (–0.8); tryptophan (–0.9); tyrosine (–1.3); proline (–1.6); histidine (–3.2); glutamate (–3.5); glutamine (–3.5); aspartate (–3.5); asparagine (–3.5); lysine (–3.9); and arginine (–4.5).

It is known in the art that certain amino acids may be substituted by other amino acids having a similar hydropathic index or score and still result in a protein with similar biological activity, *i.e.* still obtain a biological functionally equivalent protein. In making such changes, the substitution of amino acids whose hydropathic indices are within ±2 is preferred, those within ±1 are particularly preferred, and those within ±0.5 are even more particularly preferred. It is also understood in the art that the substitution of like amino acids can be made effectively on the basis of hydrophilicity. U. S. Patent 4,554,101 (specifically incorporated herein by reference in its entirety), states that the greatest local average hydrophilicity of a protein, as governed by the hydrophilicity of its adjacent amino acids, correlates with a biological property of the protein.

As detailed in U. S. Patent 4,554,101, the following hydrophilicity values have been assigned to amino acid residues: arginine (+3.0); lysine (+3.0); aspartate (+3.0 ± 1); glutamate (+3.0 ± 1); serine (+0.3); asparagine (+0.2); glutamine (+0.2); glycine (0); threonine (–0.4); proline (–0.5 ± 1); alanine (–0.5); histidine (–0.5); cysteine (–1.0); methionine (–1.3); valine (–1.5); leucine (–1.8); isoleucine (–1.8); tyrosine (–2.3); phenylalanine (–2.5); tryptophan (–3.4). It is understood that an amino acid can be substituted for another having a similar hydrophilicity value and still obtain a biologically equivalent, and in particular, an immunologically equivalent protein. In such changes, the substitution of amino acids whose hydrophilicity values are within ±2 is preferred, those within ±1 are particularly preferred, and those within ±0.5 are even more particularly preferred.

As outlined above, amino acid substitutions are generally therefore based on the relative similarity of the amino acid side-chain substituents, for example, their hydrophobicity, hydrophilicity, charge, size, and the like. Exemplary substitutions that take various of the foregoing characteristics into consideration are well known to those of skill in the art and include: arginine and lysine; glutamate and aspartate; serine and threonine; glutamine and asparagine; and valine, leucine and isoleucine.

In addition, any polynucleotide may be further modified to increase stability *in vivo*. Possible modifications include, but are not limited to, the addition of flanking sequences at the 5' and/or 3' ends; the use of phosphorothioate or 2' O-methyl rather than phosphodiesterase linkages in the backbone; and/or the inclusion of nontraditional bases such as inosine, queosine and wybutosine, as well as acetyl-methyl-, thio- and other modified forms of adenine, cytidine, guanine, thymine and uridine.

Amino acid substitutions may further be made on the basis of similarity in polarity, charge, solubility, hydrophobicity, hydrophilicity and/or the amphipathic nature of the residues. For example, negatively charged amino acids include aspartic acid and glutamic acid; positively charged amino acids include lysine and arginine; and amino acids with uncharged polar head groups having similar hydrophilicity values include leucine, isoleucine and valine; glycine and alanine; asparagine and glutamine; and serine, threonine, phenylalanine and tyrosine. Other groups of amino acids that may represent conservative changes include: (1) ala, pro, gly, glu, asp, gln, asn, ser, thr; (2) cys, ser, tyr, thr; (3) val, ile, leu, met, ala, phe; (4) lys, arg, his; and (5) phe, tyr, trp, his. A variant may also, or alternatively, contain nonconservative changes. In a preferred embodiment, variant polypeptides differ from a native sequence by substitution, deletion or addition of five amino acids or fewer. Variants may also (or alternatively) be modified by, for example, the deletion or addition of amino acids that have minimal influence on the immunogenicity, secondary structure and hydropathic nature of the polypeptide.

As noted above, polypeptides may comprise a signal (or leader) sequence at the N-terminal end of the protein, which co-translationally or post-translationally directs transfer of the protein. The polypeptide may also be conjugated to a linker or other sequence for ease of synthesis, purification or identification of the polypeptide (*e.g.*, poly-His), or to enhance binding of the polypeptide to a solid support. For example, a polypeptide may be conjugated to an immunoglobulin Fc region.

When comparing polypeptide sequences, two sequences are said to be "identical" if the sequence of amino acids in the two sequences is the same when aligned for maximum correspondence, as described below. Comparisons between two sequences are typically performed by comparing the sequences over a comparison

window to identify and compare local regions of sequence similarity. A "comparison window" as used herein, refers to a segment of at least about 20 contiguous positions, usually 30 to about 75, 40 to about 50, in which a sequence may be compared to a reference sequence of the same number of contiguous positions after the two sequences are optimally aligned.

Optimal alignment of sequences for comparison may be conducted using the Megalign program in the Lasergene suite of bioinformatics software (DNASTAR, Inc., Madison, WI), using default parameters. This program embodies several alignment schemes described in the following references: Dayhoff, M.O. (1978) A model of evolutionary change in proteins – Matrices for detecting distant relationships. In Dayhoff, M.O. (ed.) Atlas of Protein Sequence and Structure, National Biomedical Research Foundation, Washington DC Vol. 5, Suppl. 3, pp. 345-358; Hein J. (1990) Unified Approach to Alignment and Phylogenes pp. 626-645 *Methods in Enzymology* vol. 183, Academic Press, Inc., San Diego, CA; Higgins, D.G. and Sharp, P.M. (1989) *CABIOS 5*:151-153; Myers, E.W. and Muller W. (1988) *CABIOS 4*:11-17; Robinson, E.D. (1971) *Comb. Theor 11*:105; Santou, N. Nes, M. (1987) *Mol. Biol. Evol. 4*:406-425; Sneath, P.H.A. and Sokal, R.R. (1973) *Numerical Taxonomy – the Principles and Practice of Numerical Taxonomy*, Freeman Press, San Francisco, CA; Wilbur, W.J. and Lipman, D.J. (1983) *Proc. Natl. Acad., Sci. USA 80*:726-730.

Alternatively, optimal alignment of sequences for comparison may be conducted by the local identity algorithm of Smith and Waterman (1981) *Add. APL. Math* 2:482, by the identity alignment algorithm of Needleman and Wunsch (1970) *J. Mol. Biol.* 48:443, by the search for similarity methods of Pearson and Lipman (1988) *Proc. Natl. Acad. Sci. USA* 85: 2444, by computerized implementations of these algorithms (GAP, BESTFIT, BLAST, FASTA, and TFASTA in the Wisconsin Genetics Software Package, Genetics Computer Group (GCG), 575 Science Dr., Madison, WI), or by inspection.

One preferred example of algorithms that are suitable for determining percent sequence identity and sequence similarity are the BLAST and BLAST 2.0 algorithms, which are described in Altschul et al. (1977) *Nucl. Acids Res.* 25:3389-3402 and Altschul et al. (1990) *J. Mol. Biol.* 215:403-410, respectively. BLAST and BLAST 2.0 can be used, for example with the parameters described herein, to determine percent

sequence identity for the polynucleotides and polypeptides of the invention. Software for performing BLAST analyses is publicly available through the National Center for Biotechnology Information. For amino acid sequences, a scoring matrix can be used to calculate the cumulative score. Extension of the word hits in each direction are halted when: the cumulative alignment score falls off by the quantity X from its maximum achieved value; the cumulative score goes to zero or below, due to the accumulation of one or more negative-scoring residue alignments; or the end of either sequence is reached. The BLAST algorithm parameters W, T and X determine the sensitivity and speed of the alignment.

In one preferred approach, the "percentage of sequence identity" is determined by comparing two optimally aligned sequences over a window of comparison of at least 20 positions, wherein the portion of the polypeptide sequence in the comparison window may comprise additions or deletions (*i.e.*, gaps) of 20 percent or less, usually 5 to 15 percent, or 10 to 12 percent, as compared to the reference sequences (which does not comprise additions or deletions) for optimal alignment of the two sequences. The percentage is calculated by determining the number of positions at which the identical amino acid residue occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the reference sequence (*i.e.*, the window size) and multiplying the results by 100 to yield the percentage of sequence identity.

Within other illustrative embodiments, a polypeptide may be a fusion polypeptide that comprises multiple polypeptides as described herein, or that comprises at least one polypeptide as described herein and an unrelated sequence, such as a known tumor protein. A fusion partner may, for example, assist in providing T helper epitopes (an immunological fusion partner), preferably T helper epitopes recognized by humans, or may assist in expressing the protein (an expression enhancer) at higher yields than the native recombinant protein. Certain preferred fusion partners are both immunological and expression enhancing fusion partners. Other fusion partners may be selected so as to increase the solubility of the polypeptide or to enable the polypeptide to be targeted to desired intracellular compartments. Still further fusion partners include affinity tags, which facilitate purification of the polypeptide.

Fusion polypeptides may generally be prepared using standard techniques, including chemical conjugation. Preferably, a fusion polypeptide is expressed as a recombinant polypeptide, allowing the production of increased levels, relative to a non-fused polypeptide, in an expression system. Briefly, DNA sequences encoding the polypeptide components may be assembled separately, and ligated into an appropriate expression vector. The 3' end of the DNA sequence encoding one polypeptide component is ligated, with or without a peptide linker, to the 5' end of a DNA sequence encoding the second polypeptide component so that the reading frames of the sequences are in phase. This permits translation into a single fusion polypeptide that retains the biological activity of both component polypeptides.

A peptide linker sequence may be employed to separate the first and second polypeptide components by a distance sufficient to ensure that each polypeptide folds into its secondary and tertiary structures. Such a peptide linker sequence is incorporated into the fusion polypeptide using standard techniques well known in the art. Suitable peptide linker sequences may be chosen based on the following factors: (1) their ability to adopt a flexible extended conformation; (2) their inability to adopt a secondary structure that could interact with functional epitopes on the first and second polypeptides; and (3) the lack of hydrophobic or charged residues that might react with the polypeptide functional epitopes. Preferred peptide linker sequences contain Gly, Asn and Ser residues. Other near neutral amino acids, such as Thr and Ala may also be used in the linker sequence. Amino acid sequences which may be usefully employed as linkers include those disclosed in Maratea et al., *Gene 40*:39-46, 1985; Murphy et al., *Proc. Natl. Acad. Sci. USA 83*:8258-8262, 1986; U.S. Patent No. 4,935,233 and U.S. Patent No. 4,751,180. The linker sequence may generally be from 1 to about 50 amino acids in length. Linker sequences are not required when the first and second polypeptides have non-essential N-terminal amino acid regions that can be used to separate the functional domains and prevent steric interference.

The ligated DNA sequences are operably linked to suitable transcriptional or translational regulatory elements. The regulatory elements responsible for expression of DNA are located only 5' to the DNA sequence encoding the first polypeptides. Similarly, stop codons required to end translation and

transcription termination signals are only present 3' to the DNA sequence encoding the second polypeptide.

The fusion polypeptide can comprise a polypeptide as described herein together with an unrelated immunogenic protein, such as an immunogenic protein capable of eliciting a recall response. Examples of such proteins include tetanus, tuberculosis and hepatitis proteins (*see*, for example, Stoute et al. *New Engl. J. Med.*, *336*:86-91, 1997).

In one preferred embodiment, the immunological fusion partner is derived from a Mycobacterium sp., such as a Mycobacterium tuberculosis-derived Ra12 fragment. Ra12 compositions and methods for their use in enhancing the expression and/or immunogenicity of heterologous polynucleotide/polypeptide sequences is described in U.S. Patent Application 60/158,585, the disclosure of which is incorporated herein by reference in its entirety. Briefly, Ra12 refers to a polynucleotide region that is a subsequence of a *Mycobacterium tuberculosis* MTB32A nucleic acid. MTB32A is a serine protease of 32 KD molecular weight encoded by a gene in virulent and avirulent strains of *M. tuberculosis*. The nucleotide sequence and amino acid sequence of MTB32A have been described (for example, U.S. Patent Application 60/158,585; see also, Skeiky *et al.*, *Infection and Immun.* (1999) 67:3998-4007, incorporated herein by reference). C-terminal fragments of the MTB32A coding sequence express at high levels and remain as a soluble polypeptides throughout the purification process. Moreover, Ra12 may enhance the immunogenicity of heterologous immunogenic polypeptides with which it is fused. One preferred Ra12 fusion polypeptide comprises a 14 KD C-terminal fragment corresponding to amino acid residues 192 to 323 of MTB32A. Other preferred Ra12 polynucleotides generally comprise at least about 15 consecutive nucleotides, at least about 30 nucleotides, at least about 60 nucleotides, at least about 100 nucleotides, at least about 200 nucleotides, or at least about 300 nucleotides that encode a portion of a Ra12 polypeptide. Ra12 polynucleotides may comprise a native sequence (*i.e.*, an endogenous sequence that encodes a Ra12 polypeptide or a portion thereof) or may comprise a variant of such a sequence. Ra12 polynucleotide variants may contain one or more substitutions, additions, deletions and/or insertions such that the biological activity of the encoded fusion polypeptide is not substantially diminished, relative to a fusion polypeptide

comprising a native Ra12 polypeptide. Variants preferably exhibit at least about 70% identity, more preferably at least about 80% identity and most preferably at least about 90% identity to a polynucleotide sequence that encodes a native Ra12 polypeptide or a portion thereof.

Within other preferred embodiments, an immunological fusion partner is derived from protein D, a surface protein of the gram-negative bacterium Haemophilus influenza B (WO 91/18926). Preferably, a protein D derivative comprises approximately the first third of the protein (*e.g.*, the first N-terminal 100-110 amino acids), and a protein D derivative may be lipidated. Within certain preferred embodiments, the first 109 residues of a Lipoprotein D fusion partner is included on the N-terminus to provide the polypeptide with additional exogenous T-cell epitopes and to increase the expression level in *E. coli* (thus functioning as an expression enhancer). The lipid tail ensures optimal presentation of the antigen to antigen presenting cells. Other fusion partners include the non-structural protein from influenzae virus, NS1 (hemaglutinin). Typically, the N-terminal 81 amino acids are used, although different fragments that include T-helper epitopes may be used.

In another embodiment, the immunological fusion partner is the protein known as LYTA, or a portion thereof (preferably a C-terminal portion). LYTA is derived from *Streptococcus pneumoniae*, which synthesizes an N-acetyl-L-alanine amidase known as amidase LYTA (encoded by the LytA gene; *Gene 43*:265-292, 1986). LYTA is an autolysin that specifically degrades certain bonds in the peptidoglycan backbone. The C-terminal domain of the LYTA protein is responsible for the affinity to the choline or to some choline analogues such as DEAE. This property has been exploited for the development of *E. coli* C-LYTA expressing plasmids useful for expression of fusion proteins. Purification of hybrid proteins containing the C-LYTA fragment at the amino terminus has been described (*see Biotechnology 10*:795-798, 1992). Within a preferred embodiment, a repeat portion of LYTA may be incorporated into a fusion polypeptide. A repeat portion is found in the C-terminal region starting at residue 178. A particularly preferred repeat portion incorporates residues 188-305.

Yet another illustrative embodiment involves fusion polypeptides, and the polynucleotides encoding them, wherein the fusion partner comprises a targeting signal capable of directing a polypeptide to the endosomal/lysosomal compartment, as

described in U.S. Patent No. 5,633,234. An immunogenic polypeptide of the invention, when fused with this targeting signal, will associate more efficiently with MHC class II molecules and thereby provide enhanced in vivo stimulation of $CD4^+$ T-cells specific for the polypeptide.

Polypeptides of the invention are prepared using any of a variety of well known synthetic and/or recombinant techniques, the latter of which are further described below. Polypeptides, portions and other variants generally less than about 150 amino acids can be generated by synthetic means, using techniques well known to those of ordinary skill in the art. In one illustrative example, such polypeptides are synthesized using any of the commercially available solid-phase techniques, such as the Merrifield solid-phase synthesis method, where amino acids are sequentially added to a growing amino acid chain. *See* Merrifield, *J. Am. Chem. Soc. 85*:2149-2146, 1963. Equipment for automated synthesis of polypeptides is commercially available from suppliers such as Perkin Elmer/Applied BioSystems Division (Foster City, CA), and may be operated according to the manufacturer's instructions.

In general, polypeptide compositions (including fusion polypeptides) of the invention are isolated. An "isolated" polypeptide is one that is removed from its original environment. For example, a naturally-occurring protein or polypeptide is isolated if it is separated from some or all of the coexisting materials in the natural system. Preferably, such polypeptides are also purified, *e.g.*, are at least about 90% pure, more preferably at least about 95% pure and most preferably at least about 99% pure.

Polynucleotide Compositions

The present invention, in other aspects, provides polynucleotide compositions. The terms "DNA" and "polynucleotide" are used essentially interchangeably herein to refer to a DNA molecule that has been isolated free of total genomic DNA of a particular species. "Isolated," as used herein, means that a polynucleotide is substantially away from other coding sequences, and that the DNA molecule does not contain large portions of unrelated coding DNA, such as large chromosomal fragments or other functional genes or polypeptide coding regions. Of

course, this refers to the DNA molecule as originally isolated, and does not exclude genes or coding regions later added to the segment by the hand of man.

As will be understood by those skilled in the art, the polynucleotide compositions of this invention can include genomic sequences, extra-genomic and plasmid-encoded sequences and smaller engineered gene segments that express, or may be adapted to express, proteins, polypeptides, peptides and the like. Such segments may be naturally isolated, or modified synthetically by the hand of man.

As will be also recognized by the skilled artisan, polynucleotides of the invention may be single-stranded (coding or antisense) or double-stranded, and may be DNA (genomic, cDNA or synthetic) or RNA molecules. RNA molecules may include HnRNA molecules, which contain introns and correspond to a DNA molecule in a one-to-one manner, and mRNA molecules, which do not contain introns. Additional coding or non-coding sequences may, but need not, be present within a polynucleotide of the present invention, and a polynucleotide may, but need not, be linked to other molecules and/or support materials.

Polynucleotides may comprise a native sequence (*i.e.*, an endogenous sequence that encodes a polypeptide/protein of the invention or a portion thereof) or may comprise a sequence that encodes a variant or derivative, preferably and immunogenic variant or derivative, of such a sequence.

Therefore, according to another aspect of the present invention, polynucleotide compositions are provided that comprise some or all of a polynucleotide sequence set forth in any one of SEQ ID NOs: 1-232, 243-396, 398-412, 414-424 and 437-440, complements of a polynucleotide sequence set forth in any one of SEQ ID NOs: 1-232, 243-396, 398-412, 414-424 and 437-440, and degenerate variants of a polynucleotide sequence set forth in any one of SEQ ID NOs: 1-232, 243-396, 398-412, 414-424 and 437-440. In certain preferred embodiments, the polynucleotide sequences set forth herein encode immunogenic polypeptides, as described above.

In other related embodiments, the present invention provides polynucleotide variants having substantial identity to the sequences disclosed herein in SEQ ID NOs: 1-232, 243-396, 398-412, 414-424 and 437-440, for example those comprising at least 70% sequence identity, preferably at least 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% or higher, sequence identity compared to a

polynucleotide sequence of this invention using the methods described herein, (*e.g.*, BLAST analysis using standard parameters, as described below). One skilled in this art will recognize that these values can be appropriately adjusted to determine corresponding identity of proteins encoded by two nucleotide sequences by taking into account codon degeneracy, amino acid similarity, reading frame positioning and the like.

Typically, polynucleotide variants will contain one or more substitutions, additions, deletions and/or insertions, preferably such that the immunogenicity of the polypeptide encoded by the variant polynucleotide is not substantially diminished relative to a polypeptide encoded by a polynucleotide sequence specifically set forth herein). The term "variants" should also be understood to encompasses homologous genes of xenogenic origin.

In additional embodiments, the present invention provides polynucleotide fragments comprising various lengths of contiguous stretches of sequence identical to or complementary to one or more of the sequences disclosed herein. For example, polynucleotides are provided by this invention that comprise at least about 10, 15, 20, 30, 40, 50, 75, 100, 150, 200, 300, 400, 500 or 1000 or more contiguous nucleotides of one or more of the sequences disclosed herein as well as all intermediate lengths there between. It will be readily understood that "intermediate lengths", in this context, means any length between the quoted values, such as 16, 17, 18, 19, *etc.*; 21, 22, 23, *etc.*; 30, 31, 32, *etc.*; 50, 51, 52, 53, *etc.*; 100, 101, 102, 103, *etc.*; 150, 151, 152, 153, *etc.*; including all integers through 200-500; 500-1,000, and the like.

In another embodiment of the invention, polynucleotide compositions are provided that are capable of hybridizing under moderate to high stringency conditions to a polynucleotide sequence provided herein, or a fragment thereof, or a complementary sequence thereof. Hybridization techniques are well known in the art of molecular biology. For purposes of illustration, suitable moderately stringent conditions for testing the hybridization of a polynucleotide of this invention with other polynucleotides include prewashing in a solution of 5 X SSC, 0.5% SDS, 1.0 mM EDTA (pH 8.0); hybridizing at 50°C-60°C, 5 X SSC, overnight; followed by washing twice at 65°C for 20 minutes with each of 2X, 0.5X and 0.2X SSC containing 0.1% SDS. One skilled in

the art will understand that the stringency of hybridization can be readily manipulated, such as by altering the salt content of the hybridization solution and/or the temperature at which the hybridization is performed. For example, in another embodiment, suitable highly stringent hybridization conditions include those described above, with the exception that the temperature of hybridization is increased, *e.g.*, to 60-65°C or 65-70°C.

In certain preferred embodiments, the polynucleotides described above, *e.g.*, polynucleotide variants, fragments and hybridizing sequences, encode polypeptides that are immunologically cross-reactive with a polypeptide sequence specifically set forth herein. In other preferred embodiments, such polynucleotides encode polypeptides that have a level of immunogenic activity of at least about 50%, preferably at least about 70%, and more preferably at least about 90% of that for a polypeptide sequence specifically set forth herein.

The polynucleotides of the present invention, or fragments thereof, regardless of the length of the coding sequence itself, may be combined with other DNA sequences, such as promoters, polyadenylation signals, additional restriction enzyme sites, multiple cloning sites, other coding segments, and the like, such that their overall length may vary considerably. It is therefore contemplated that a nucleic acid fragment of almost any length may be employed, with the total length preferably being limited by the ease of preparation and use in the intended recombinant DNA protocol. For example, illustrative polynucleotide segments with total lengths of about 10,000, about 5000, about 3000, about 2,000, about 1,000, about 500, about 200, about 100, about 50 base pairs in length, and the like, (including all intermediate lengths) are contemplated to be useful in many implementations of this invention.

When comparing polynucleotide sequences, two sequences are said to be "identical" if the sequence of nucleotides in the two sequences is the same when aligned for maximum correspondence, as described below. Comparisons between two sequences are typically performed by comparing the sequences over a comparison window to identify and compare local regions of sequence similarity. A "comparison window" as used herein, refers to a segment of at least about 20 contiguous positions, usually 30 to about 75, 40 to about 50, in which a sequence may be compared to a

reference sequence of the same number of contiguous positions after the two sequences are optimally aligned.

Optimal alignment of sequences for comparison may be conducted using the Megalign program in the Lasergene suite of bioinformatics software (DNASTAR, Inc., Madison, WI), using default parameters. This program embodies several alignment schemes described in the following references: Dayhoff, M.O. (1978) A model of evolutionary change in proteins – Matrices for detecting distant relationships. In Dayhoff, M.O. (ed.) Atlas of Protein Sequence and Structure, National Biomedical Research Foundation, Washington DC Vol. 5, Suppl. 3, pp. 345-358; Hein J. (1990) Unified Approach to Alignment and Phylogenes pp. 626-645 *Methods in Enzymology* vol. 183, Academic Press, Inc., San Diego, CA; Higgins, D.G. and Sharp, P.M. (1989) *CABIOS 5*:151-153; Myers, E.W. and Muller W. (1988) *CABIOS 4*:11-17; Robinson, E.D. (1971) *Comb. Theor 11*:105; Santou, N. Nes, M. (1987) *Mol. Biol. Evol. 4*:406-425; Sneath, P.H.A. and Sokal, R.R. (1973) *Numerical Taxonomy – the Principles and Practice of Numerical Taxonomy*, Freeman Press, San Francisco, CA; Wilbur, W.J. and Lipman, D.J. (1983) *Proc. Natl. Acad., Sci. USA 80*:726-730.

Alternatively, optimal alignment of sequences for comparison may be conducted by the local identity algorithm of Smith and Waterman (1981) *Add. APL. Math* 2:482, by the identity alignment algorithm of Needleman and Wunsch (1970) *J. Mol. Biol.* 48:443, by the search for similarity methods of Pearson and Lipman (1988) *Proc. Natl. Acad. Sci. USA* 85: 2444, by computerized implementations of these algorithms (GAP, BESTFIT, BLAST, FASTA, and TFASTA in the Wisconsin Genetics Software Package, Genetics Computer Group (GCG), 575 Science Dr., Madison, WI), or by inspection.

One preferred example of algorithms that are suitable for determining percent sequence identity and sequence similarity are the BLAST and BLAST 2.0 algorithms, which are described in Altschul et al. (1977) *Nucl. Acids Res.* 25:3389-3402 and Altschul et al. (1990) *J. Mol. Biol.* 215:403-410, respectively. BLAST and BLAST 2.0 can be used, for example with the parameters described herein, to determine percent sequence identity for the polynucleotides of the invention. Software for performing BLAST analyses is publicly available through the National Center for Biotechnology Information. In one illustrative example, cumulative scores can be calculated using, for

nucleotide sequences, the parameters M (reward score for a pair of matching residues; always >0) and N (penalty score for mismatching residues; always <0). Extension of the word hits in each direction are halted when: the cumulative alignment score falls off by the quantity X from its maximum achieved value; the cumulative score goes to zero or below, due to the accumulation of one or more negative-scoring residue alignments; or the end of either sequence is reached. The BLAST algorithm parameters W, T and X determine the sensitivity and speed of the alignment. The BLASTN program (for nucleotide sequences) uses as defaults a wordlength (W) of 11, and expectation (E) of 10, and the BLOSUM62 scoring matrix (see Henikoff and Henikoff (1989) *Proc. Natl. Acad. Sci. USA* 89:10915) alignments, (B) of 50, expectation (E) of 10, M=5, N=-4 and a comparison of both strands.

Preferably, the "percentage of sequence identity" is determined by comparing two optimally aligned sequences over a window of comparison of at least 20 positions, wherein the portion of the polynucleotide sequence in the comparison window may comprise additions or deletions (*i.e.*, gaps) of 20 percent or less, usually 5 to 15 percent, or 10 to 12 percent, as compared to the reference sequences (which does not comprise additions or deletions) for optimal alignment of the two sequences. The percentage is calculated by determining the number of positions at which the identical nucleic acid bases occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the reference sequence (*i.e.*, the window size) and multiplying the results by 100 to yield the percentage of sequence identity.

It will be appreciated by those of ordinary skill in the art that, as a result of the degeneracy of the genetic code, there are many nucleotide sequences that encode a polypeptide as described herein. Some of these polynucleotides bear minimal homology to the nucleotide sequence of any native gene. Nonetheless, polynucleotides that vary due to differences in codon usage are specifically contemplated by the present invention. Further, alleles of the genes comprising the polynucleotide sequences provided herein are within the scope of the present invention. Alleles are endogenous genes that are altered as a result of one or more mutations, such as deletions, additions and/or substitutions of nucleotides. The resulting mRNA and protein may, but need not,

have an altered structure or function. Alleles may be identified using standard techniques (such as hybridization, amplification and/or database sequence comparison).

Therefore, in another embodiment of the invention, a mutagenesis approach, such as site-specific mutagenesis, is employed for the preparation of immunogenic variants and/or derivatives of the polypeptides described herein. By this approach, specific modifications in a polypeptide sequence can be made through mutagenesis of the underlying polynucleotides that encode them. These techniques provides a straightforward approach to prepare and test sequence variants, for example, incorporating one or more of the foregoing considerations, by introducing one or more nucleotide sequence changes into the polynucleotide.

Site-specific mutagenesis allows the production of mutants through the use of specific oligonucleotide sequences which encode the DNA sequence of the desired mutation, as well as a sufficient number of adjacent nucleotides, to provide a primer sequence of sufficient size and sequence complexity to form a stable duplex on both sides of the deletion junction being traversed. Mutations may be employed in a selected polynucleotide sequence to improve, alter, decrease, modify, or otherwise change the properties of the polynucleotide itself, and/or alter the properties, activity, composition, stability, or primary sequence of the encoded polypeptide.

In certain embodiments of the present invention, the inventors contemplate the mutagenesis of the disclosed polynucleotide sequences to alter one or more properties of the encoded polypeptide, such as the immunogenicity of a polypeptide vaccine. The techniques of site-specific mutagenesis are well-known in the art, and are widely used to create variants of both polypeptides and polynucleotides. For example, site-specific mutagenesis is often used to alter a specific portion of a DNA molecule. In such embodiments, a primer comprising typically about 14 to about 25 nucleotides or so in length is employed, with about 5 to about 10 residues on both sides of the junction of the sequence being altered.

As will be appreciated by those of skill in the art, site-specific mutagenesis techniques have often employed a phage vector that exists in both a single stranded and double stranded form. Typical vectors useful in site-directed mutagenesis include vectors such as the M13 phage. These phage are readily commercially-available and their use is generally well-known to those skilled in the art. Double-stranded

plasmids are also routinely employed in site directed mutagenesis that eliminates the step of transferring the gene of interest from a plasmid to a phage.

In general, site-directed mutagenesis in accordance herewith is performed by first obtaining a single-stranded vector or melting apart of two strands of a double-stranded vector that includes within its sequence a DNA sequence that encodes the desired peptide. An oligonucleotide primer bearing the desired mutated sequence is prepared, generally synthetically. This primer is then annealed with the single-stranded vector, and subjected to DNA polymerizing enzymes such as *E. coli* polymerase I Klenow fragment, in order to complete the synthesis of the mutation-bearing strand. Thus, a heteroduplex is formed wherein one strand encodes the original non-mutated sequence and the second strand bears the desired mutation. This heteroduplex vector is then used to transform appropriate cells, such as *E. coli* cells, and clones are selected which include recombinant vectors bearing the mutated sequence arrangement.

The preparation of sequence variants of the selected peptide-encoding DNA segments using site-directed mutagenesis provides a means of producing potentially useful species and is not meant to be limiting as there are other ways in which sequence variants of peptides and the DNA sequences encoding them may be obtained. For example, recombinant vectors encoding the desired peptide sequence may be treated with mutagenic agents, such as hydroxylamine, to obtain sequence variants. Specific details regarding these methods and protocols are found in the teachings of Maloy *et al.*, 1994; Segal, 1976; Prokop and Bajpai, 1991; Kuby, 1994; and Maniatis *et al.*, 1982, each incorporated herein by reference, for that purpose.

As used herein, the term "oligonucleotide directed mutagenesis procedure" refers to template-dependent processes and vector-mediated propagation which result in an increase in the concentration of a specific nucleic acid molecule relative to its initial concentration, or in an increase in the concentration of a detectable signal, such as amplification. As used herein, the term "oligonucleotide directed mutagenesis procedure" is intended to refer to a process that involves the template-dependent extension of a primer molecule. The term template dependent process refers to nucleic acid synthesis of an RNA or a DNA molecule wherein the sequence of the newly synthesized strand of nucleic acid is dictated by the well-known rules of complementary base pairing (see, for example, Watson, 1987). Typically,

vector mediated methodologies involve the introduction of the nucleic acid fragment into a DNA or RNA vector, the clonal amplification of the vector, and the recovery of the amplified nucleic acid fragment. Examples of such methodologies are provided by U. S. Patent No. 4,237,224, specifically incorporated herein by reference in its entirety.

In another approach for the production of polypeptide variants of the present invention, recursive sequence recombination, as described in U.S. Patent No. 5,837,458, may be employed. In this approach, iterative cycles of recombination and screening or selection are performed to "evolve" individual polynucleotide variants of the invention having, for example, enhanced immunogenic activity.

In other embodiments of the present invention, the polynucleotide sequences provided herein can be advantageously used as probes or primers for nucleic acid hybridization. As such, it is contemplated that nucleic acid segments that comprise a sequence region of at least about 15 nucleotide long contiguous sequence that has the same sequence as, or is complementary to, a 15 nucleotide long contiguous sequence disclosed herein will find particular utility. Longer contiguous identical or complementary sequences, *e.g.*, those of about 20, 30, 40, 50, 100, 200, 500, 1000 (including all intermediate lengths) and even up to full length sequences will also be of use in certain embodiments.

The ability of such nucleic acid probes to specifically hybridize to a sequence of interest will enable them to be of use in detecting the presence of complementary sequences in a given sample. However, other uses are also envisioned, such as the use of the sequence information for the preparation of mutant species primers, or primers for use in preparing other genetic constructions.

Polynucleotide molecules having sequence regions consisting of contiguous nucleotide stretches of 10-14, 15-20, 30, 50, or even of 100-200 nucleotides or so (including intermediate lengths as well), identical or complementary to a polynucleotide sequence disclosed herein, are particularly contemplated as hybridization probes for use in, *e.g.*, Southern and Northern blotting. This would allow a gene product, or fragment thereof, to be analyzed, both in diverse cell types and also in various bacterial cells. The total size of fragment, as well as the size of the complementary stretch(es), will ultimately depend on the intended use or application of the particular nucleic acid segment. Smaller fragments will generally find use in

hybridization embodiments, wherein the length of the contiguous complementary region may be varied, such as between about 15 and about 100 nucleotides, but larger contiguous complementarity stretches may be used, according to the length complementary sequences one wishes to detect.

The use of a hybridization probe of about 15-25 nucleotides in length allows the formation of a duplex molecule that is both stable and selective. Molecules having contiguous complementary sequences over stretches greater than 15 bases in length are generally preferred, though, in order to increase stability and selectivity of the hybrid, and thereby improve the quality and degree of specific hybrid molecules obtained. One will generally prefer to design nucleic acid molecules having gene-complementary stretches of 15 to 25 contiguous nucleotides, or even longer where desired.

Hybridization probes may be selected from any portion of any of the sequences disclosed herein. All that is required is to review the sequences set forth herein, or to any continuous portion of the sequences, from about 15-25 nucleotides in length up to and including the full length sequence, that one wishes to utilize as a probe or primer. The choice of probe and primer sequences may be governed by various factors. For example, one may wish to employ primers from towards the termini of the total sequence.

Small polynucleotide segments or fragments may be readily prepared by, for example, directly synthesizing the fragment by chemical means, as is commonly practiced using an automated oligonucleotide synthesizer. Also, fragments may be obtained by application of nucleic acid reproduction technology, such as the PCR™ technology of U. S. Patent 4,683,202 (incorporated herein by reference), by introducing selected sequences into recombinant vectors for recombinant production, and by other recombinant DNA techniques generally known to those of skill in the art of molecular biology.

The nucleotide sequences of the invention may be used for their ability to selectively form duplex molecules with complementary stretches of the entire gene or gene fragments of interest. Depending on the application envisioned, one will typically desire to employ varying conditions of hybridization to achieve varying degrees of selectivity of probe towards target sequence. For applications requiring high selectivity,

one will typically desire to employ relatively stringent conditions to form the hybrids, *e.g.*, one will select relatively low salt and/or high temperature conditions, such as provided by a salt concentration of from about 0.02 M to about 0.15 M salt at temperatures of from about 50°C to about 70°C. Such selective conditions tolerate little, if any, mismatch between the probe and the template or target strand, and would be particularly suitable for isolating related sequences.

Of course, for some applications, for example, where one desires to prepare mutants employing a mutant primer strand hybridized to an underlying template, less stringent (reduced stringency) hybridization conditions will typically be needed in order to allow formation of the heteroduplex. In these circumstances, one may desire to employ salt conditions such as those of from about 0.15 M to about 0.9 M salt, at temperatures ranging from about 20°C to about 55°C. Cross-hybridizing species can thereby be readily identified as positively hybridizing signals with respect to control hybridizations. In any case, it is generally appreciated that conditions can be rendered more stringent by the addition of increasing amounts of formamide, which serves to destabilize the hybrid duplex in the same manner as increased temperature. Thus, hybridization conditions can be readily manipulated, and thus will generally be a method of choice depending on the desired results.

According to another embodiment of the present invention, polynucleotide compositions comprising antisense oligonucleotides are provided. Antisense oligonucleotides have been demonstrated to be effective and targeted inhibitors of protein synthesis, and, consequently, provide a therapeutic approach by which a disease can be treated by inhibiting the synthesis of proteins that contribute to the disease. The efficacy of antisense oligonucleotides for inhibiting protein synthesis is well established. For example, the synthesis of polygalactauronase and the muscarine type 2 acetylcholine receptor are inhibited by antisense oligonucleotides directed to their respective mRNA sequences (U. S. Patent 5,739,119 and U. S. Patent 5,759,829). Further, examples of antisense inhibition have been demonstrated with the nuclear protein cyclin, the multiple drug resistance gene (MDG1), ICAM-1, E-selectin, STK-1, striatal $GABA_A$ receptor and human EGF (Jaskulski *et al.*, Science. 1988 Jun 10;240(4858):1544-6; Vasanthakumar and Ahmed, Cancer Commun. 1989;1(4):225-32; Peris *et al.*, Brain Res Mol Brain Res. 1998 Jun 15;57(2):310-20; U. S. Patent

5,801,154; U.S. Patent 5,789,573; U. S. Patent 5,718,709 and U.S. Patent 5,610,288). Antisense constructs have also been described that inhibit and can be used to treat a variety of abnormal cellular proliferations, *e.g.* cancer (U. S. Patent 5,747,470; U. S. Patent 5,591,317 and U. S. Patent 5,783,683).

Therefore, in certain embodiments, the present invention provides oligonucleotide sequences that comprise all, or a portion of, any sequence that is capable of specifically binding to polynucleotide sequence described herein, or a complement thereof. In one embodiment, the antisense oligonucleotides comprise DNA or derivatives thereof. In another embodiment, the oligonucleotides comprise RNA or derivatives thereof. In a third embodiment, the oligonucleotides are modified DNAs comprising a phosphorothioated modified backbone. In a fourth embodiment, the oligonucleotide sequences comprise peptide nucleic acids or derivatives thereof. In each case, preferred compositions comprise a sequence region that is complementary, and more preferably substantially-complementary, and even more preferably, completely complementary to one or more portions of polynucleotides disclosed herein. Selection of antisense compositions specific for a given gene sequence is based upon analysis of the chosen target sequence and determination of secondary structure, T_m, binding energy, and relative stability. Antisense compositions may be selected based upon their relative inability to form dimers, hairpins, or other secondary structures that would reduce or prohibit specific binding to the target mRNA in a host cell. Highly preferred target regions of the mRNA, are those which are at or near the AUG translation initiation codon, and those sequences which are substantially complementary to 5' regions of the mRNA. These secondary structure analyses and target site selection considerations can be performed, for example, using v.4 of the OLIGO primer analysis software and/or the BLASTN 2.0.5 algorithm software (Altschul *et al.*, Nucleic Acids Res. 1997, 25(17):3389-402).

The use of an antisense delivery method employing a short peptide vector, termed MPG (27 residues), is also contemplated. The MPG peptide contains a hydrophobic domain derived from the fusion sequence of HIV gp41 and a hydrophilic domain from the nuclear localization sequence of SV40 T-antigen (Morris *et al.*, Nucleic Acids Res. 1997 Jul 15;25(14):2730-6). It has been demonstrated that several molecules of the MPG peptide coat the antisense oligonucleotides and can be delivered

into cultured mammalian cells in less than 1 hour with relatively high efficiency (90%). Further, the interaction with MPG strongly increases both the stability of the oligonucleotide to nuclease and the ability to cross the plasma membrane.

According to another embodiment of the invention, the polynucleotide compositions described herein are used in the design and preparation of ribozyme molecules for inhibiting expression of the tumor polypeptides and proteins of the present invention in tumor cells. Ribozymes are RNA-protein complexes that cleave nucleic acids in a site-specific fashion. Ribozymes have specific catalytic domains that possess endonuclease activity (Kim and Cech, Proc Natl Acad Sci U S A. 1987 Dec;84(24):8788-92; Forster and Symons, Cell. 1987 Apr 24;49(2):211-20). For example, a large number of ribozymes accelerate phosphoester transfer reactions with a high degree of specificity, often cleaving only one of several phosphoesters in an oligonucleotide substrate (Cech *et al.*, Cell. 1981 Dec;27(3 Pt 2):487-96; Michel and Westhof, J Mol Biol. 1990 Dec 5;216(3):585-610; Reinhold-Hurek and Shub, Nature. 1992 May 14;357(6374):173-6). This specificity has been attributed to the requirement that the substrate bind via specific base-pairing interactions to the internal guide sequence ("IGS") of the ribozyme prior to chemical reaction.

Six basic varieties of naturally-occurring enzymatic RNAs are known presently. Each can catalyze the hydrolysis of RNA phosphodiester bonds *in trans* (and thus can cleave other RNA molecules) under physiological conditions. In general, enzymatic nucleic acids act by first binding to a target RNA. Such binding occurs through the target binding portion of a enzymatic nucleic acid which is held in close proximity to an enzymatic portion of the molecule that acts to cleave the target RNA. Thus, the enzymatic nucleic acid first recognizes and then binds a target RNA through complementary base-pairing, and once bound to the correct site, acts enzymatically to cut the target RNA. Strategic cleavage of such a target RNA will destroy its ability to direct synthesis of an encoded protein. After an enzymatic nucleic acid has bound and cleaved its RNA target, it is released from that RNA to search for another target and can repeatedly bind and cleave new targets.

The enzymatic nature of a ribozyme is advantageous over many technologies, such as antisense technology (where a nucleic acid molecule simply binds to a nucleic acid target to block its translation) since the concentration of ribozyme

necessary to affect a therapeutic treatment is lower than that of an antisense oligonucleotide. This advantage reflects the ability of the ribozyme to act enzymatically. Thus, a single ribozyme molecule is able to cleave many molecules of target RNA. In addition, the ribozyme is a highly specific inhibitor, with the specificity of inhibition depending not only on the base pairing mechanism of binding to the target RNA, but also on the mechanism of target RNA cleavage. Single mismatches, or base-substitutions, near the site of cleavage can completely eliminate catalytic activity of a ribozyme. Similar mismatches in antisense molecules do not prevent their action (Woolf *et al.*, Proc Natl Acad Sci U S A. 1992 Aug 15;89(16):7305-9). Thus, the specificity of action of a ribozyme is greater than that of an antisense oligonucleotide binding the same RNA site.

The enzymatic nucleic acid molecule may be formed in a hammerhead, hairpin, a hepatitis δ virus, group I intron or RNaseP RNA (in association with an RNA guide sequence) or Neurospora VS RNA motif. Examples of hammerhead motifs are described by Rossi *et al.* Nucleic Acids Res. 1992 Sep 11;20(17):4559-65. Examples of hairpin motifs are described by Hampel *et al.* (Eur. Pat. Appl. Publ. No. EP 0360257), Hampel and Tritz, Biochemistry 1989 Jun 13;28(12):4929-33; Hampel *et al.*, Nucleic Acids Res. 1990 Jan 25;18(2):299-304 and U. S. Patent 5,631,359. An example of the hepatitis δ virus motif is described by Perrotta and Been, Biochemistry. 1992 Dec 1;31(47):11843-52; an example of the RNaseP motif is described by Guerrier-Takada *et al.*, Cell. 1983 Dec;35(3 Pt 2):849-57; Neurospora VS RNA ribozyme motif is described by Collins (Saville and Collins, Cell. 1990 May 18;61(4):685-96; Saville and Collins, Proc Natl Acad Sci U S A. 1991 Oct 1;88(19):8826-30; Collins and Olive, Biochemistry. 1993 Mar 23;32(11):2795-9); and an example of the Group I intron is described in (U. S. Patent 4,987,071). All that is important in an enzymatic nucleic acid molecule of this invention is that it has a specific substrate binding site which is complementary to one or more of the target gene RNA regions, and that it have nucleotide sequences within or surrounding that substrate binding site which impart an RNA cleaving activity to the molecule. Thus the ribozyme constructs need not be limited to specific motifs mentioned herein.

Ribozymes may be designed as described in Int. Pat. Appl. Publ. No. WO 93/23569 and Int. Pat. Appl. Publ. No. WO 94/02595, each specifically

incorporated herein by reference) and synthesized to be tested *in vitro* and *in vivo*, as described. Such ribozymes can also be optimized for delivery. While specific examples are provided, those in the art will recognize that equivalent RNA targets in other species can be utilized when necessary.

Ribozyme activity can be optimized by altering the length of the ribozyme binding arms, or chemically synthesizing ribozymes with modifications that prevent their degradation by serum ribonucleases (see *e.g.*, Int. Pat. Appl. Publ. No. WO 92/07065; Int. Pat. Appl. Publ. No. WO 93/15187; Int. Pat. Appl. Publ. No. WO 91/03162; Eur. Pat. Appl. Publ. No. 92110298.4; U. S. Patent 5,334,711; and Int. Pat. Appl. Publ. No. WO 94/13688, which describe various chemical modifications that can be made to the sugar moieties of enzymatic RNA molecules), modifications which enhance their efficacy in cells, and removal of stem II bases to shorten RNA synthesis times and reduce chemical requirements.

Sullivan *et al.* (Int. Pat. Appl. Publ. No. WO 94/02595) describes the general methods for delivery of enzymatic RNA molecules. Ribozymes may be administered to cells by a variety of methods known to those familiar to the art, including, but not restricted to, encapsulation in liposomes, by iontophoresis, or by incorporation into other vehicles, such as hydrogels, cyclodextrins, biodegradable nanocapsules, and bioadhesive microspheres. For some indications, ribozymes may be directly delivered *ex vivo* to cells or tissues with or without the aforementioned vehicles. Alternatively, the RNA/vehicle combination may be locally delivered by direct inhalation, by direct injection or by use of a catheter; infusion pump or stent. Other routes of delivery include, but are not limited to, intravascular, intramuscular, subcutaneous or joint injection, aerosol inhalation, oral (tablet or pill form), topical, systemic, ocular, intraperitoneal and/or intrathecal delivery. More detailed descriptions of ribozyme delivery and administration are provided in Int. Pat. Appl. Publ. No. WO 94/02595 and Int. Pat. Appl. Publ. No. WO 93/23569, each specifically incorporated herein by reference.

Another means of accumulating high concentrations of a ribozyme(s) within cells is to incorporate the ribozyme-encoding sequences into a DNA expression vector. Transcription of the ribozyme sequences are driven from a promoter for eukaryotic RNA polymerase I (pol I), RNA polymerase II (pol II), or RNA polymerase

III (pol III). Transcripts from pol II or pol III promoters will be expressed at high levels in all cells; the levels of a given pol II promoter in a given cell type will depend on the nature of the gene regulatory sequences (enhancers, silencers, *etc.*) present nearby. Prokaryotic RNA polymerase promoters may also be used, providing that the prokaryotic RNA polymerase enzyme is expressed in the appropriate cells Ribozymes expressed from such promoters have been shown to function in mammalian cells. Such transcription units can be incorporated into a variety of vectors for introduction into mammalian cells, including but not restricted to, plasmid DNA vectors, viral DNA vectors (such as adenovirus or adeno-associated vectors), or viral RNA vectors (such as retroviral, semliki forest virus, sindbis virus vectors).

In another embodiment of the invention, peptide nucleic acids (PNAs) compositions are provided. PNA is a DNA mimic in which the nucleobases are attached to a pseudopeptide backbone (Good and Nielsen, Antisense Nucleic Acid Drug Dev. 1997 7(4) 431-37). PNA is able to be utilized in a number methods that traditionally have used RNA or DNA. Often PNA sequences perform better in techniques than the corresponding RNA or DNA sequences and have utilities that are not inherent to RNA or DNA. A review of PNA including methods of making, characteristics of, and methods of using, is provided by Corey (*Trends Biotechnol* 1997 Jun;15(6):224-9). As such, in certain embodiments, one may prepare PNA sequences that are complementary to one or more portions of the ACE mRNA sequence, and such PNA compositions may be used to regulate, alter, decrease, or reduce the translation of ACE-specific mRNA, and thereby alter the level of ACE activity in a host cell to which such PNA compositions have been administered.

PNAs have 2-aminoethyl-glycine linkages replacing the normal phosphodiester backbone of DNA (Nielsen *et al.*, *Science* 1991 Dec 6;254(5037):1497-500; Hanvey *et al.*, Science. 1992 Nov 27;258(5087):1481-5; Hyrup and Nielsen, Bioorg Med Chem. 1996 Jan;4(1):5-23). This chemistry has three important consequences: firstly, in contrast to DNA or phosphorothioate oligonucleotides, PNAs are neutral molecules; secondly, PNAs are achiral, which avoids the need to develop a stereoselective synthesis; and thirdly, PNA synthesis uses standard Boc or Fmoc protocols for solid-phase peptide synthesis, although other methods, including a modified Merrifield method, have been used.

PNA monomers or ready-made oligomers are commercially available from PerSeptive Biosystems (Framingham, MA). PNA syntheses by either Boc or Fmoc protocols are straightforward using manual or automated protocols (Norton *et al.*, Bioorg Med Chem. 1995 Apr;3(4):437-45). The manual protocol lends itself to the production of chemically modified PNAs or the simultaneous synthesis of families of closely related PNAs.

As with peptide synthesis, the success of a particular PNA synthesis will depend on the properties of the chosen sequence. For example, while in theory PNAs can incorporate any combination of nucleotide bases, the presence of adjacent purines can lead to deletions of one or more residues in the product. In expectation of this difficulty, it is suggested that, in producing PNAs with adjacent purines, one should repeat the coupling of residues likely to be added inefficiently. This should be followed by the purification of PNAs by reverse-phase high-pressure liquid chromatography, providing yields and purity of product similar to those observed during the synthesis of peptides.

Modifications of PNAs for a given application may be accomplished by coupling amino acids during solid-phase synthesis or by attaching compounds that contain a carboxylic acid group to the exposed N-terminal amine. Alternatively, PNAs can be modified after synthesis by coupling to an introduced lysine or cysteine. The ease with which PNAs can be modified facilitates optimization for better solubility or for specific functional requirements. Once synthesized, the identity of PNAs and their derivatives can be confirmed by mass spectrometry. Several studies have made and utilized modifications of PNAs (for example, Norton *et al.*, Bioorg Med Chem. 1995 Apr;3(4):437-45; Petersen *et al.*, J Pept Sci. 1995 May-Jun;1(3):175-83; Orum *et al.*, Biotechniques. 1995 Sep;19(3):472-80; Footer *et al.*, Biochemistry. 1996 Aug 20;35(33):10673-9; Griffith *et al.*, Nucleic Acids Res. 1995 Aug 11;23(15):3003-8; Pardridge *et al.*, Proc Natl Acad Sci U S A. 1995 Jun 6;92(12):5592-6; Boffa *et al.*, Proc Natl Acad Sci U S A. 1995 Mar 14;92(6):1901-5; Gambacorti-Passerini *et al.*, Blood. 1996 Aug 15;88(4):1411-7; Armitage *et al.*, Proc Natl Acad Sci U S A. 1997 Nov 11;94(23):12320-5; Seeger *et al.*, Biotechniques. 1997 Sep;23(3):512-7). U.S. Patent No. 5,700,922 discusses PNA-DNA-PNA chimeric molecules and their uses in

diagnostics, modulating protein in organisms, and treatment of conditions susceptible to therapeutics.

Methods of characterizing the antisense binding properties of PNAs are discussed in Rose (Anal Chem. 1993 Dec 15;65(24):3545-9) and Jensen *et al.* (Biochemistry. 1997 Apr 22;36(16):5072-7). Rose uses capillary gel electrophoresis to determine binding of PNAs to their complementary oligonucleotide, measuring the relative binding kinetics and stoichiometry. Similar types of measurements were made by Jensen *et al.* using BIAcore™ technology.

Other applications of PNAs that have been described and will be apparent to the skilled artisan include use in DNA strand invasion, antisense inhibition, mutational analysis, enhancers of transcription, nucleic acid purification, isolation of transcriptionally active genes, blocking of transcription factor binding, genome cleavage, biosensors, *in situ* hybridization, and the like.

Polynucleotide Identification, Characterization and Expression

Polynucleotides compositions of the present invention may be identified, prepared and/or manipulated using any of a variety of well established techniques (see generally, Sambrook et al., *Molecular Cloning: A Laboratory Manual,* Cold Spring Harbor Laboratories, Cold Spring Harbor, NY, 1989, and other like references). For example, a polynucleotide may be identified, as described in more detail below, by screening a microarray of cDNAs for tumor-associated expression (*i.e.,* expression that is at least two fold greater in a tumor than in normal tissue, as determined using a representative assay provided herein). Such screens may be performed, for example, using the microarray technology of Affymetrix, Inc. (Santa Clara, CA) according to the manufacturer's instructions (and essentially as described by Schena et al., *Proc. Natl. Acad. Sci. USA 93*:10614-10619, 1996 and Heller et al., *Proc. Natl. Acad. Sci. USA 94*:2150-2155, 1997). Alternatively, polynucleotides may be amplified from cDNA prepared from cells expressing the proteins described herein, such as tumor cells.

Many template dependent processes are available to amplify a target sequences of interest present in a sample. One of the best known amplification methods is the polymerase chain reaction (PCR™) which is described in detail in U.S. Patent Nos. 4,683,195, 4,683,202 and 4,800,159, each of which is incorporated herein by

reference in its entirety. Briefly, in PCR™, two primer sequences are prepared which are complementary to regions on opposite complementary strands of the target sequence. An excess of deoxynucleoside triphosphates is added to a reaction mixture along with a DNA polymerase (*e.g.*, *Taq* polymerase). If the target sequence is present in a sample, the primers will bind to the target and the polymerase will cause the primers to be extended along the target sequence by adding on nucleotides. By raising and lowering the temperature of the reaction mixture, the extended primers will dissociate from the target to form reaction products, excess primers will bind to the target and to the reaction product and the process is repeated. Preferably reverse transcription and PCR™ amplification procedure may be performed in order to quantify the amount of mRNA amplified. Polymerase chain reaction methodologies are well known in the art.

Any of a number of other template dependent processes, many of which are variations of the PCR ™ amplification technique, are readily known and available in the art. Illustratively, some such methods include the ligase chain reaction (referred to as LCR), described, for example, in Eur. Pat. Appl. Publ. No. 320,308 and U.S. Patent No. 4,883,750; Qbeta Replicase, described in PCT Intl. Pat. Appl. Publ. No. PCT/US87/00880; Strand Displacement Amplification (SDA) and Repair Chain Reaction (RCR). Still other amplification methods are described in Great Britain Pat. Appl. No. 2 202 328, and in PCT Intl. Pat. Appl. Publ. No. PCT/US89/01025. Other nucleic acid amplification procedures include transcription-based amplification systems (TAS) (PCT Intl. Pat. Appl. Publ. No. WO 88/10315), including nucleic acid sequence based amplification (NASBA) and 3SR. Eur. Pat. Appl. Publ. No. 329,822 describes a nucleic acid amplification process involving cyclically synthesizing single-stranded RNA ("ssRNA"), ssDNA, and double-stranded DNA (dsDNA). PCT Intl. Pat. Appl. Publ. No. WO 89/06700 describes a nucleic acid sequence amplification scheme based on the hybridization of a promoter/primer sequence to a target single-stranded DNA ("ssDNA") followed by transcription of many RNA copies of the sequence. Other amplification methods such as "RACE" (Frohman, 1990), and "one-sided PCR" (Ohara, 1989) are also well-known to those of skill in the art.

An amplified portion of a polynucleotide of the present invention may be used to isolate a full length gene from a suitable library (*e.g.*, a tumor cDNA library)

using well known techniques. Within such techniques, a library (cDNA or genomic) is screened using one or more polynucleotide probes or primers suitable for amplification. Preferably, a library is size-selected to include larger molecules. Random primed libraries may also be preferred for identifying 5' and upstream regions of genes. Genomic libraries are preferred for obtaining introns and extending 5' sequences.

For hybridization techniques, a partial sequence may be labeled (*e.g.*, by nick-translation or end-labeling with ^{32}P) using well known techniques. A bacterial or bacteriophage library is then generally screened by hybridizing filters containing denatured bacterial colonies (or lawns containing phage plaques) with the labeled probe (*see* Sambrook et al., *Molecular Cloning: A Laboratory Manual,* Cold Spring Harbor Laboratories, Cold Spring Harbor, NY, 1989). Hybridizing colonies or plaques are selected and expanded, and the DNA is isolated for further analysis. cDNA clones may be analyzed to determine the amount of additional sequence by, for example, PCR using a primer from the partial sequence and a primer from the vector. Restriction maps and partial sequences may be generated to identify one or more overlapping clones. The complete sequence may then be determined using standard techniques, which may involve generating a series of deletion clones. The resulting overlapping sequences can then assembled into a single contiguous sequence. A full length cDNA molecule can be generated by ligating suitable fragments, using well known techniques.

Alternatively, amplification techniques, such as those described above, can be useful for obtaining a full length coding sequence from a partial cDNA sequence. One such amplification technique is inverse PCR (*see* Triglia et al., *Nucl. Acids Res. 16*:8186, 1988), which uses restriction enzymes to generate a fragment in the known region of the gene. The fragment is then circularized by intramolecular ligation and used as a template for PCR with divergent primers derived from the known region. Within an alternative approach, sequences adjacent to a partial sequence may be retrieved by amplification with a primer to a linker sequence and a primer specific to a known region. The amplified sequences are typically subjected to a second round of amplification with the same linker primer and a second primer specific to the known region. A variation on this procedure, which employs two primers that initiate extension in opposite directions from the known sequence, is described in WO 96/38591. Another such technique is known as "rapid amplification of cDNA ends" or

RACE. This technique involves the use of an internal primer and an external primer, which hybridizes to a polyA region or vector sequence, to identify sequences that are 5' and 3' of a known sequence. Additional techniques include capture PCR (Lagerstrom et al., *PCR Methods Applic. 1*:111-19, 1991) and walking PCR (Parker et al., *Nucl. Acids. Res. 19*:3055-60, 1991). Other methods employing amplification may also be employed to obtain a full length cDNA sequence.

In certain instances, it is possible to obtain a full length cDNA sequence by analysis of sequences provided in an expressed sequence tag (EST) database, such as that available from GenBank. Searches for overlapping ESTs may generally be performed using well known programs (*e.g.*, NCBI BLAST searches), and such ESTs may be used to generate a contiguous full length sequence. Full length DNA sequences may also be obtained by analysis of genomic fragments.

In other embodiments of the invention, polynucleotide sequences or fragments thereof which encode polypeptides of the invention, or fusion proteins or functional equivalents thereof, may be used in recombinant DNA molecules to direct expression of a polypeptide in appropriate host cells. Due to the inherent degeneracy of the genetic code, other DNA sequences that encode substantially the same or a functionally equivalent amino acid sequence may be produced and these sequences may be used to clone and express a given polypeptide.

As will be understood by those of skill in the art, it may be advantageous in some instances to produce polypeptide-encoding nucleotide sequences possessing non-naturally occurring codons. For example, codons preferred by a particular prokaryotic or eukaryotic host can be selected to increase the rate of protein expression or to produce a recombinant RNA transcript having desirable properties, such as a half-life which is longer than that of a transcript generated from the naturally occurring sequence.

Moreover, the polynucleotide sequences of the present invention can be engineered using methods generally known in the art in order to alter polypeptide encoding sequences for a variety of reasons, including but not limited to, alterations which modify the cloning, processing, and/or expression of the gene product. For example, DNA shuffling by random fragmentation and PCR reassembly of gene fragments and synthetic oligonucleotides may be used to engineer the nucleotide

sequences. In addition, site-directed mutagenesis may be used to insert new restriction sites, alter glycosylation patterns, change codon preference, produce splice variants, or introduce mutations, and so forth.

In another embodiment of the invention, natural, modified, or recombinant nucleic acid sequences may be ligated to a heterologous sequence to encode a fusion protein. For example, to screen peptide libraries for inhibitors of polypeptide activity, it may be useful to encode a chimeric protein that can be recognized by a commercially available antibody. A fusion protein may also be engineered to contain a cleavage site located between the polypeptide-encoding sequence and the heterologous protein sequence, so that the polypeptide may be cleaved and purified away from the heterologous moiety.

Sequences encoding a desired polypeptide may be synthesized, in whole or in part, using chemical methods well known in the art (see Caruthers, M. H. et al. (1980) *Nucl. Acids Res. Symp. Ser.* 215-223, Horn, T. et al. (1980) *Nucl. Acids Res. Symp. Ser.* 225-232). Alternatively, the protein itself may be produced using chemical methods to synthesize the amino acid sequence of a polypeptide, or a portion thereof. For example, peptide synthesis can be performed using various solid-phase techniques (Roberge, J. Y. et al. (1995) *Science 269*:202-204) and automated synthesis may be achieved, for example, using the ABI 431A Peptide Synthesizer (Perkin Elmer, Palo Alto, CA).

A newly synthesized peptide may be substantially purified by preparative high performance liquid chromatography (*e.g.*, Creighton, T. (1983) Proteins, Structures and Molecular Principles, WH Freeman and Co., New York, N.Y.) or other comparable techniques available in the art. The composition of the synthetic peptides may be confirmed by amino acid analysis or sequencing (*e.g.*, the Edman degradation procedure). Additionally, the amino acid sequence of a polypeptide, or any part thereof, may be altered during direct synthesis and/or combined using chemical methods with sequences from other proteins, or any part thereof, to produce a variant polypeptide.

In order to express a desired polypeptide, the nucleotide sequences encoding the polypeptide, or functional equivalents, may be inserted into appropriate expression vector, *i.e.*, a vector which contains the necessary elements for the transcription and translation of the inserted coding sequence. Methods which are well

known to those skilled in the art may be used to construct expression vectors containing sequences encoding a polypeptide of interest and appropriate transcriptional and translational control elements. These methods include *in vitro* recombinant DNA techniques, synthetic techniques, and *in vivo* genetic recombination. Such techniques are described, for example, in Sambrook, J. et al. (1989) Molecular Cloning, A Laboratory Manual, Cold Spring Harbor Press, Plainview, N.Y., and Ausubel, F. M. et al. (1989) Current Protocols in Molecular Biology, John Wiley & Sons, New York. N.Y.

A variety of expression vector/host systems may be utilized to contain and express polynucleotide sequences. These include, but are not limited to, microorganisms such as bacteria transformed with recombinant bacteriophage, plasmid, or cosmid DNA expression vectors; yeast transformed with yeast expression vectors; insect cell systems infected with virus expression vectors (*e.g.*, baculovirus); plant cell systems transformed with virus expression vectors (*e.g.*, cauliflower mosaic virus, CaMV; tobacco mosaic virus, TMV) or with bacterial expression vectors (*e.g.*, Ti or pBR322 plasmids); or animal cell systems.

The "control elements" or "regulatory sequences" present in an expression vector are those non-translated regions of the vector--enhancers, promoters, 5' and 3' untranslated regions--which interact with host cellular proteins to carry out transcription and translation. Such elements may vary in their strength and specificity. Depending on the vector system and host utilized, any number of suitable transcription and translation elements, including constitutive and inducible promoters, may be used. For example, when cloning in bacterial systems, inducible promoters such as the hybrid lacZ promoter of the PBLUESCRIPT phagemid (Stratagene, La Jolla, Calif.) or PSPORT1 plasmid (Gibco BRL, Gaithersburg, MD) and the like may be used. In mammalian cell systems, promoters from mammalian genes or from mammalian viruses are generally preferred. If it is necessary to generate a cell line that contains multiple copies of the sequence encoding a polypeptide, vectors based on SV40 or EBV may be advantageously used with an appropriate selectable marker.

In bacterial systems, any of a number of expression vectors may be selected depending upon the use intended for the expressed polypeptide. For example, when large quantities are needed, for example for the induction of antibodies, vectors

which direct high level expression of fusion proteins that are readily purified may be used. Such vectors include, but are not limited to, the multifunctional *E. coli* cloning and expression vectors such as BLUESCRIPT (Stratagene), in which the sequence encoding the polypeptide of interest may be ligated into the vector in frame with sequences for the amino-terminal Met and the subsequent 7 residues of .beta.-galactosidase so that a hybrid protein is produced; pIN vectors (Van Heeke, G. and S. M. Schuster (1989) *J. Biol. Chem. 264*:5503-5509); and the like. pGEX Vectors (Promega, Madison, Wis.) may also be used to express foreign polypeptides as fusion proteins with glutathione S-transferase (GST). In general, such fusion proteins are soluble and can easily be purified from lysed cells by adsorption to glutathione-agarose beads followed by elution in the presence of free glutathione. Proteins made in such systems may be designed to include heparin, thrombin, or factor XA protease cleavage sites so that the cloned polypeptide of interest can be released from the GST moiety at will.

In the yeast, Saccharomyces cerevisiae, a number of vectors containing constitutive or inducible promoters such as alpha factor, alcohol oxidase, and PGH may be used. For reviews, see Ausubel et al. (supra) and Grant et al. (1987) *Methods Enzymol.* 153:516-544.

In cases where plant expression vectors are used, the expression of sequences encoding polypeptides may be driven by any of a number of promoters. For example, viral promoters such as the 35S and 19S promoters of CaMV may be used alone or in combination with the omega leader sequence from TMV (Takamatsu, N. (1987) *EMBO J. 6*:307-311. Alternatively, plant promoters such as the small subunit of RUBISCO or heat shock promoters may be used (Coruzzi, G. et al. (1984) *EMBO J. 3*:1671-1680; Broglie, R. et al. (1984) *Science 224*:838-843; and Winter, J. et al. (1991) *Results Probl. Cell Differ. 17*:85-105). These constructs can be introduced into plant cells by direct DNA transformation or pathogen-mediated transfection. Such techniques are described in a number of generally available reviews (see, for example, Hobbs, S. or Murry, L. E. in McGraw Hill Yearbook of Science and Technology (1992) McGraw Hill, New York, N.Y.; pp. 191-196).

An insect system may also be used to express a polypeptide of interest. For example, in one such system, Autographa californica nuclear polyhedrosis virus

(AcNPV) is used as a vector to express foreign genes in Spodoptera frugiperda cells or in Trichoplusia larvae. The sequences encoding the polypeptide may be cloned into a non-essential region of the virus, such as the polyhedrin gene, and placed under control of the polyhedrin promoter. Successful insertion of the polypeptide-encoding sequence will render the polyhedrin gene inactive and produce recombinant virus lacking coat protein. The recombinant viruses may then be used to infect, for example, S. frugiperda cells or Trichoplusia larvae in which the polypeptide of interest may be expressed (Engelhard, E. K. et al. (1994) *Proc. Natl. Acad. Sci. 91* :3224-3227).

In mammalian host cells, a number of viral-based expression systems are generally available. For example, in cases where an adenovirus is used as an expression vector, sequences encoding a polypeptide of interest may be ligated into an adenovirus transcription/translation complex consisting of the late promoter and tripartite leader sequence. Insertion in a non-essential E1 or E3 region of the viral genome may be used to obtain a viable virus which is capable of expressing the polypeptide in infected host cells (Logan, J. and Shenk, T. (1984) *Proc. Natl. Acad. Sci. 81*:3655-3659). In addition, transcription enhancers, such as the Rous sarcoma virus (RSV) enhancer, may be used to increase expression in mammalian host cells.

Specific initiation signals may also be used to achieve more efficient translation of sequences encoding a polypeptide of interest. Such signals include the ATG initiation codon and adjacent sequences. In cases where sequences encoding the polypeptide, its initiation codon, and upstream sequences are inserted into the appropriate expression vector, no additional transcriptional or translational control signals may be needed. However, in cases where only coding sequence, or a portion thereof, is inserted, exogenous translational control signals including the ATG initiation codon should be provided. Furthermore, the initiation codon should be in the correct reading frame to ensure translation of the entire insert. Exogenous translational elements and initiation codons may be of various origins, both natural and synthetic. The efficiency of expression may be enhanced by the inclusion of enhancers which are appropriate for the particular cell system which is used, such as those described in the literature (Scharf, D. et al. (1994) *Results Probl. Cell Differ. 20*:125-162).

In addition, a host cell strain may be chosen for its ability to modulate the expression of the inserted sequences or to process the expressed protein in the

desired fashion. Such modifications of the polypeptide include, but are not limited to, acetylation, carboxylation. glycosylation, phosphorylation, lipidation, and acylation. Post-translational processing which cleaves a "prepro" form of the protein may also be used to facilitate correct insertion, folding and/or function. Different host cells such as CHO, COS, HeLa, MDCK, HEK293, and WI38, which have specific cellular machinery and characteristic mechanisms for such post-translational activities, may be chosen to ensure the correct modification and processing of the foreign protein.

For long-term, high-yield production of recombinant proteins, stable expression is generally preferred. For example, cell lines which stably express a polynucleotide of interest may be transformed using expression vectors which may contain viral origins of replication and/or endogenous expression elements and a selectable marker gene on the same or on a separate vector. Following the introduction of the vector, cells may be allowed to grow for 1-2 days in an enriched media before they are switched to selective media. The purpose of the selectable marker is to confer resistance to selection, and its presence allows growth and recovery of cells which successfully express the introduced sequences. Resistant clones of stably transformed cells may be proliferated using tissue culture techniques appropriate to the cell type.

Any number of selection systems may be used to recover transformed cell lines. These include, but are not limited to, the herpes simplex virus thymidine kinase (Wigler, M. et al. (1977) *Cell 11*:223-32) and adenine phosphoribosyltransferase (Lowy, I. et al. (1990) *Cell 22*:817-23) genes which can be employed in tk.sup.- or aprt.sup.- cells, respectively. Also, antimetabolite, antibiotic or herbicide resistance can be used as the basis for selection; for example, dhfr which confers resistance to methotrexate (Wigler, M. et al. (1980) *Proc. Natl. Acad. Sci. 77*:3567-70); npt, which confers resistance to the aminoglycosides, neomycin and G-418 (Colbere-Garapin, F. et al (1981) *J. Mol. Biol. 150*:1-14); and als or pat, which confer resistance to chlorsulfuron and phosphinotricin acetyltransferase, respectively (Murry, *supra*). Additional selectable genes have been described, for example, trpB, which allows cells to utilize indole in place of tryptophan, or hisD, which allows cells to utilize histinol in place of histidine (Hartman, S. C. and R. C. Mulligan (1988) *Proc. Natl. Acad. Sci. 85*:8047-51). The use of visible markers has gained popularity with such markers as anthocyanins, beta-glucuronidase and its substrate GUS, and luciferase and its substrate

luciferin, being widely used not only to identify transformants, but also to quantify the amount of transient or stable protein expression attributable to a specific vector system (Rhodes, C. A. et al. (1995) *Methods Mol. Biol. 55*:121-131).

Although the presence/absence of marker gene expression suggests that the gene of interest is also present, its presence and expression may need to be confirmed. For example, if the sequence encoding a polypeptide is inserted within a marker gene sequence, recombinant cells containing sequences can be identified by the absence of marker gene function. Alternatively, a marker gene can be placed in tandem with a polypeptide-encoding sequence under the control of a single promoter. Expression of the marker gene in response to induction or selection usually indicates expression of the tandem gene as well.

Alternatively, host cells that contain and express a desired polynucleotide sequence may be identified by a variety of procedures known to those of skill in the art. These procedures include, but are not limited to, DNA-DNA or DNA-RNA hybridizations and protein bioassay or immunoassay techniques which include, for example, membrane, solution, or chip based technologies for the detection and/or quantification of nucleic acid or protein.

A variety of protocols for detecting and measuring the expression of polynucleotide-encoded products, using either polyclonal or monoclonal antibodies specific for the product are known in the art. Examples include enzyme-linked immunosorbent assay (ELISA), radioimmunoassay (RIA), and fluorescence activated cell sorting (FACS). A two-site, monoclonal-based immunoassay utilizing monoclonal antibodies reactive to two non-interfering epitopes on a given polypeptide may be preferred for some applications, but a competitive binding assay may also be employed. These and other assays are described, among other places, in Hampton, R. et al. (1990; Serological Methods, a Laboratory Manual, APS Press, St Paul. Minn.) and Maddox, D. E. et al. (1983; *J. Exp. Med. 158*:1211-1216).

A wide variety of labels and conjugation techniques are known by those skilled in the art and may be used in various nucleic acid and amino acid assays. Means for producing labeled hybridization or PCR probes for detecting sequences related to polynucleotides include oligolabeling, nick translation, end-labeling or PCR amplification using a labeled nucleotide. Alternatively, the sequences, or any portions

thereof may be cloned into a vector for the production of an mRNA probe. Such vectors are known in the art, are commercially available, and may be used to synthesize RNA probes in vitro by addition of an appropriate RNA polymerase such as T7, T3, or SP6 and labeled nucleotides. These procedures may be conducted using a variety of commercially available kits. Suitable reporter molecules or labels, which may be used include radionuclides, enzymes, fluorescent, chemiluminescent, or chromogenic agents as well as substrates, cofactors, inhibitors, magnetic particles, and the like.

Host cells transformed with a polynucleotide sequence of interest may be cultured under conditions suitable for the expression and recovery of the protein from cell culture. The protein produced by a recombinant cell may be secreted or contained intracellularly depending on the sequence and/or the vector used. As will be understood by those of skill in the art, expression vectors containing polynucleotides of the invention may be designed to contain signal sequences which direct secretion of the encoded polypeptide through a prokaryotic or eukaryotic cell membrane. Other recombinant constructions may be used to join sequences encoding a polypeptide of interest to nucleotide sequence encoding a polypeptide domain which will facilitate purification of soluble proteins. Such purification facilitating domains include, but are not limited to, metal chelating peptides such as histidine-tryptophan modules that allow purification on immobilized metals, protein A domains that allow purification on immobilized immunoglobulin, and the domain utilized in the FLAGS extension/affinity purification system (Immunex Corp., Seattle, Wash.). The inclusion of cleavable linker sequences such as those specific for Factor XA or enterokinase (Invitrogen. San Diego, Calif.) between the purification domain and the encoded polypeptide may be used to facilitate purification. One such expression vector provides for expression of a fusion protein containing a polypeptide of interest and a nucleic acid encoding 6 histidine residues preceding a thioredoxin or an enterokinase cleavage site. The histidine residues facilitate purification on IMIAC (immobilized metal ion affinity chromatography) as described in Porath, J. et al. (1992, *Prot. Exp. Purif. 3*:263-281) while the enterokinase cleavage site provides a means for purifying the desired polypeptide from the fusion protein. A discussion of vectors which contain fusion proteins is provided in Kroll, D. J. et al. (1993; *DNA Cell Biol. 12*:441-453).

In addition to recombinant production methods, polypeptides of the invention, and fragments thereof, may be produced by direct peptide synthesis using solid-phase techniques (Merrifield J. (1963) *J. Am. Chem. Soc. 85*:2149-2154). Protein synthesis may be performed using manual techniques or by automation. Automated synthesis may be achieved, for example, using Applied Biosystems 431A Peptide Synthesizer (Perkin Elmer). Alternatively, various fragments may be chemically synthesized separately and combined using chemical methods to produce the full length molecule.

Antibody Compositions, Fragments Thereof and Other Binding Agents

According to another aspect, the present invention further provides binding agents, such as antibodies and antigen-binding fragments thereof, that exhibit immunological binding to a tumor polypeptide disclosed herein, or to a portion, variant or derivative thereof. An antibody, or antigen-binding fragment thereof, is said to "specifically bind," "immunogically bind," and/or is "immunologically reactive" to a polypeptide of the invention if it reacts at a detectable level (within, for example, an ELISA assay) with the polypeptide, and does not react detectably with unrelated polypeptides under similar conditions.

Immunological binding, as used in this context, generally refers to the non-covalent interactions of the type which occur between an immunoglobulin molecule and an antigen for which the immunoglobulin is specific. The strength, or affinity of immunological binding interactions can be expressed in terms of the dissociation constant (K_d) of the interaction, wherein a smaller K_d represents a greater affinity. Immunological binding properties of selected polypeptides can be quantified using methods well known in the art. One such method entails measuring the rates of antigen-binding site/antigen complex formation and dissociation, wherein those rates depend on the concentrations of the complex partners, the affinity of the interaction, and on geometric parameters that equally influence the rate in both directions. Thus, both the "on rate constant" (K_{on}) and the "off rate constant" (K_{off}) can be determined by calculation of the concentrations and the actual rates of association and dissociation. The ratio of K_{off}/K_{on} enables cancellation of all parameters not related to affinity, and is

thus equal to the dissociation constant K_d. See, generally, Davies et al. (1990) Annual Rev. Biochem. 59:439-473.

An "antigen-binding site," or "binding portion" of an antibody refers to the part of the immunoglobulin molecule that participates in antigen binding. The antigen binding site is formed by amino acid residues of the N-terminal variable ("V") regions of the heavy ("H") and light ("L") chains. Three highly divergent stretches within the V regions of the heavy and light chains are referred to as "hypervariable regions" which are interposed between more conserved flanking stretches known as "framework regions," or "FRs". Thus the term "FR" refers to amino acid sequences which are naturally found between and adjacent to hypervariable regions in immunoglobulins. In an antibody molecule, the three hypervariable regions of a light chain and the three hypervariable regions of a heavy chain are disposed relative to each other in three dimensional space to form an antigen-binding surface. The antigen-binding surface is complementary to the three-dimensional surface of a bound antigen, and the three hypervariable regions of each of the heavy and light chains are referred to as "complementarity-determining regions," or "CDRs."

Binding agents may be further capable of differentiating between patients with and without a cancer, such as lung cancer, using the representative assays provided herein. For example, antibodies or other binding agents that bind to a tumor protein will preferably generate a signal indicating the presence of a cancer in at least about 20% of patients with the disease, more preferably at least about 30% of patients. Alternatively, or in addition, the antibody will generate a negative signal indicating the absence of the disease in at least about 90% of individuals without the cancer. To determine whether a binding agent satisfies this requirement, biological samples (*e.g.*, blood, sera, sputum, urine and/or tumor biopsies) from patients with and without a cancer (as determined using standard clinical tests) may be assayed as described herein for the presence of polypeptides that bind to the binding agent. Preferably, a statistically significant number of samples with and without the disease will be assayed. Each binding agent should satisfy the above criteria; however, those of ordinary skill in the art will recognize that binding agents may be used in combination to improve sensitivity.

Any agent that satisfies the above requirements may be a binding agent. For example, a binding agent may be a ribosome, with or without a peptide component, an RNA molecule or a polypeptide. In a preferred embodiment, a binding agent is an antibody or an antigen-binding fragment thereof. Antibodies may be prepared by any of a variety of techniques known to those of ordinary skill in the art. *See, e.g.,* Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, 1988. In general, antibodies can be produced by cell culture techniques, including the generation of monoclonal antibodies as described herein, or via transfection of antibody genes into suitable bacterial or mammalian cell hosts, in order to allow for the production of recombinant antibodies. In one technique, an immunogen comprising the polypeptide is initially injected into any of a wide variety of mammals (*e.g.,* mice, rats, rabbits, sheep or goats). In this step, the polypeptides of this invention may serve as the immunogen without modification. Alternatively, particularly for relatively short polypeptides, a superior immune response may be elicited if the polypeptide is joined to a carrier protein, such as bovine serum albumin or keyhole limpet hemocyanin. The immunogen is injected into the animal host, preferably according to a predetermined schedule incorporating one or more booster immunizations, and the animals are bled periodically. Polyclonal antibodies specific for the polypeptide may then be purified from such antisera by, for example, affinity chromatography using the polypeptide coupled to a suitable solid support.

Monoclonal antibodies specific for an antigenic polypeptide of interest may be prepared, for example, using the technique of Kohler and Milstein, *Eur. J. Immunol. 6*:511-519, 1976, and improvements thereto. Briefly, these methods involve the preparation of immortal cell lines capable of producing antibodies having the desired specificity (*i.e.*, reactivity with the polypeptide of interest). Such cell lines may be produced, for example, from spleen cells obtained from an animal immunized as described above. The spleen cells are then immortalized by, for example, fusion with a myeloma cell fusion partner, preferably one that is syngeneic with the immunized animal. A variety of fusion techniques may be employed. For example, the spleen cells and myeloma cells may be combined with a nonionic detergent for a few minutes and then plated at low density on a selective medium that supports the growth of hybrid cells, but not myeloma cells. A preferred selection technique uses HAT (hypoxanthine,

aminopterin, thymidine) selection. After a sufficient time, usually about 1 to 2 weeks, colonies of hybrids are observed. Single colonies are selected and their culture supernatants tested for binding activity against the polypeptide. Hybridomas having high reactivity and specificity are preferred.

Monoclonal antibodies may be isolated from the supernatants of growing hybridoma colonies. In addition, various techniques may be employed to enhance the yield, such as injection of the hybridoma cell line into the peritoneal cavity of a suitable vertebrate host, such as a mouse. Monoclonal antibodies may then be harvested from the ascites fluid or the blood. Contaminants may be removed from the antibodies by conventional techniques, such as chromatography, gel filtration, precipitation, and extraction. The polypeptides of this invention may be used in the purification process in, for example, an affinity chromatography step.

A number of therapeutically useful molecules are known in the art which comprise antigen-binding sites that are capable of exhibiting immunological binding properties of an antibody molecule. The proteolytic enzyme papain preferentially cleaves IgG molecules to yield several fragments, two of which (the "F(ab)" fragments) each comprise a covalent heterodimer that includes an intact antigen-binding site. The enzyme pepsin is able to cleave IgG molecules to provide several fragments, including the "$F(ab')_2$ " fragment which comprises both antigen-binding sites. An "Fv" fragment can be produced by preferential proteolytic cleavage of an IgM, and on rare occasions IgG or IgA immunoglobulin molecule. Fv fragments are, however, more commonly derived using recombinant techniques known in the art. The Fv fragment includes a non-covalent $V_H::V_L$ heterodimer including an antigen-binding site which retains much of the antigen recognition and binding capabilities of the native antibody molecule. Inbar et al. (1972) Proc. Nat. Acad. Sci. USA 69:2659-2662; Hochman et al. (1976) Biochem 15:2706-2710; and Ehrlich et al. (1980) Biochem 19:4091-4096.

A single chain Fv ("sFv") polypeptide is a covalently linked $V_H::V_L$ heterodimer which is expressed from a gene fusion including V_H- and V_L-encoding genes linked by a peptide-encoding linker. Huston et al. (1988) Proc. Nat. Acad. Sci. USA 85(16):5879-5883. A number of methods have been described to discern chemical structures for converting the naturally aggregated--but chemically separated--light and heavy polypeptide chains from an antibody V region into an sFv molecule which will

fold into a three dimensional structure substantially similar to the structure of an antigen-binding site. See, *e.g.*, U.S. Pat. Nos. 5,091,513 and 5,132,405, to Huston et al.; and U.S. Pat. No. 4,946,778, to Ladner et al.

Each of the above-described molecules includes a heavy chain and a light chain CDR set, respectively interposed between a heavy chain and a light chain FR set which provide support to the CDRS and define the spatial relationship of the CDRs relative to each other. As used herein, the term "CDR set" refers to the three hypervariable regions of a heavy or light chain V region. Proceeding from the N-terminus of a heavy or light chain, these regions are denoted as "CDR1," "CDR2," and "CDR3" respectively. An antigen-binding site, therefore, includes six CDRs, comprising the CDR set from each of a heavy and a light chain V region. A polypeptide comprising a single CDR, (*e.g.*, a CDR1, CDR2 or CDR3) is referred to herein as a "molecular recognition unit." Crystallographic analysis of a number of antigen-antibody complexes has demonstrated that the amino acid residues of CDRs form extensive contact with bound antigen, wherein the most extensive antigen contact is with the heavy chain CDR3. Thus, the molecular recognition units are primarily responsible for the specificity of an antigen-binding site.

As used herein, the term "FR set" refers to the four flanking amino acid sequences which frame the CDRs of a CDR set of a heavy or light chain V region. Some FR residues may contact bound antigen; however, FRs are primarily responsible for folding the V region into the antigen-binding site, particularly the FR residues directly adjacent to the CDRS. Within FRs, certain amino residues and certain structural features are very highly conserved. In this regard, all V region sequences contain an internal disulfide loop of around 90 amino acid residues. When the V regions fold into a binding-site, the CDRs are displayed as projecting loop motifs which form an antigen-binding surface. It is generally recognized that there are conserved structural regions of FRs which influence the folded shape of the CDR loops into certain "canonical" structures--regardless of the precise CDR amino acid sequence. Further, certain FR residues are known to participate in non-covalent interdomain contacts which stabilize the interaction of the antibody heavy and light chains.

A number of "humanized" antibody molecules comprising an antigen-binding site derived from a non-human immunoglobulin have been described, including

chimeric antibodies having rodent V regions and their associated CDRs fused to human constant domains (Winter et al. (1991) Nature 349:293-299; Lobuglio et al. (1989) Proc. Nat. Acad. Sci. USA 86:4220-4224; Shaw et al. (1987) J Immunol. 138:4534-4538; and Brown et al. (1987) Cancer Res. 47:3577-3583), rodent CDRs grafted into a human supporting FR prior to fusion with an appropriate human antibody constant domain (Riechmann et al. (1988) Nature 332:323-327; Verhoeyen et al. (1988) Science 239:1534-1536; and Jones et al. (1986) Nature 321:522-525), and rodent CDRs supported by recombinantly veneered rodent FRs (European Patent Publication No. 519,596, published Dec. 23, 1992). These "humanized" molecules are designed to minimize unwanted immunological response toward rodent antihuman antibody molecules which limits the duration and effectiveness of therapeutic applications of those moieties in human recipients.

As used herein, the terms "veneered FRs" and "recombinantly veneered FRs" refer to the selective replacement of FR residues from, *e.g.*, a rodent heavy or light chain V region, with human FR residues in order to provide a xenogeneic molecule comprising an antigen-binding site which retains substantially all of the native FR polypeptide folding structure. Veneering techniques are based on the understanding that the ligand binding characteristics of an antigen-binding site are determined primarily by the structure and relative disposition of the heavy and light chain CDR sets within the antigen-binding surface. Davies et al. (1990) Ann. Rev. Biochem. 59:439-473. Thus, antigen binding specificity can be preserved in a humanized antibody only wherein the CDR structures, their interaction with each other, and their interaction with the rest of the V region domains are carefully maintained. By using veneering techniques, exterior (*e.g.*, solvent-accessible) FR residues which are readily encountered by the immune system are selectively replaced with human residues to provide a hybrid molecule that comprises either a weakly immunogenic, or substantially non-immunogenic veneered surface.

The process of veneering makes use of the available sequence data for human antibody variable domains compiled by Kabat et al., in Sequences of Proteins of Immunological Interest, 4th ed., (U.S. Dept. of Health and Human Services, U.S. Government Printing Office, 1987), updates to the Kabat database, and other accessible U.S. and foreign databases (both nucleic acid and protein). Solvent accessibilities of V

region amino acids can be deduced from the known three-dimensional structure for human and murine antibody fragments. There are two general steps in veneering a murine antigen-binding site. Initially, the FRs of the variable domains of an antibody molecule of interest are compared with corresponding FR sequences of human variable domains obtained from the above-identified sources. The most homologous human V regions are then compared residue by residue to corresponding murine amino acids. The residues in the murine FR which differ from the human counterpart are replaced by the residues present in the human moiety using recombinant techniques well known in the art. Residue switching is only carried out with moieties which are at least partially exposed (solvent accessible), and care is exercised in the replacement of amino acid residues which may have a significant effect on the tertiary structure of V region domains, such as proline, glycine and charged amino acids.

In this manner, the resultant "veneered" murine antigen-binding sites are thus designed to retain the murine CDR residues, the residues substantially adjacent to the CDRs, the residues identified as buried or mostly buried (solvent inaccessible), the residues believed to participate in non-covalent (*e.g.*, electrostatic and hydrophobic) contacts between heavy and light chain domains, and the residues from conserved structural regions of the FRs which are believed to influence the "canonical" tertiary structures of the CDR loops. These design criteria are then used to prepare recombinant nucleotide sequences which combine the CDRs of both the heavy and light chain of a murine antigen-binding site into human-appearing FRs that can be used to transfect mammalian cells for the expression of recombinant human antibodies which exhibit the antigen specificity of the murine antibody molecule.

In another embodiment of the invention, monoclonal antibodies of the present invention may be coupled to one or more therapeutic agents. Suitable agents in this regard include radionuclides, differentiation inducers, drugs, toxins, and derivatives thereof. Preferred radionuclides include ^{90}Y, ^{123}I, ^{125}I, ^{131}I, ^{186}Re, ^{188}Re, ^{211}At, and ^{212}Bi. Preferred drugs include methotrexate, and pyrimidine and purine analogs. Preferred differentiation inducers include phorbol esters and butyric acid. Preferred toxins include ricin, abrin, diptheria toxin, cholera toxin, gelonin, Pseudomonas exotoxin, Shigella toxin, and pokeweed antiviral protein.

A therapeutic agent may be coupled (*e.g.*, covalently bonded) to a suitable monoclonal antibody either directly or indirectly (*e.g.*, via a linker group). A direct reaction between an agent and an antibody is possible when each possesses a substituent capable of reacting with the other. For example, a nucleophilic group, such as an amino or sulfhydryl group, on one may be capable of reacting with a carbonyl-containing group, such as an anhydride or an acid halide, or with an alkyl group containing a good leaving group (*e.g.*, a halide) on the other.

Alternatively, it may be desirable to couple a therapeutic agent and an antibody via a linker group. A linker group can function as a spacer to distance an antibody from an agent in order to avoid interference with binding capabilities. A linker group can also serve to increase the chemical reactivity of a substituent on an agent or an antibody, and thus increase the coupling efficiency. An increase in chemical reactivity may also facilitate the use of agents, or functional groups on agents, which otherwise would not be possible.

It will be evident to those skilled in the art that a variety of bifunctional or polyfunctional reagents, both homo- and hetero-functional (such as those described in the catalog of the Pierce Chemical Co., Rockford, IL), may be employed as the linker group. Coupling may be effected, for example, through amino groups, carboxyl groups, sulfhydryl groups or oxidized carbohydrate residues. There are numerous references describing such methodology, *e.g.*, U.S. Patent No. 4,671,958, to Rodwell et al.

Where a therapeutic agent is more potent when free from the antibody portion of the immunoconjugates of the present invention, it may be desirable to use a linker group which is cleavable during or upon internalization into a cell. A number of different cleavable linker groups have been described. The mechanisms for the intracellular release of an agent from these linker groups include cleavage by reduction of a disulfide bond (*e.g.*, U.S. Patent No. 4,489,710, to Spitler), by irradiation of a photolabile bond (*e.g.*, U.S. Patent No. 4,625,014, to Senter et al.), by hydrolysis of derivatized amino acid side chains (*e.g.*, U.S. Patent No. 4,638,045, to Kohn et al.), by serum complement-mediated hydrolysis (*e.g.*, U.S. Patent No. 4,671,958, to Rodwell et al.), and acid-catalyzed hydrolysis (*e.g.*, U.S. Patent No. 4,569,789, to Blattler et al.).

It may be desirable to couple more than one agent to an antibody. In one embodiment, multiple molecules of an agent are coupled to one antibody molecule. In

another embodiment, more than one type of agent may be coupled to one antibody. Regardless of the particular embodiment, immunoconjugates with more than one agent may be prepared in a variety of ways. For example, more than one agent may be coupled directly to an antibody molecule, or linkers that provide multiple sites for attachment can be used. Alternatively, a carrier can be used.

A carrier may bear the agents in a variety of ways, including covalent bonding either directly or via a linker group. Suitable carriers include proteins such as albumins (*e.g.*, U.S. Patent No. 4,507,234, to Kato et al.), peptides and polysaccharides such as aminodextran (*e.g.*, U.S. Patent No. 4,699,784, to Shih et al.). A carrier may also bear an agent by noncovalent bonding or by encapsulation, such as within a liposome vesicle (*e.g.*, U.S. Patent Nos. 4,429,008 and 4,873,088). Carriers specific for radionuclide agents include radiohalogenated small molecules and chelating compounds. For example, U.S. Patent No. 4,735,792 discloses representative radiohalogenated small molecules and their synthesis. A radionuclide chelate may be formed from chelating compounds that include those containing nitrogen and sulfur atoms as the donor atoms for binding the metal, or metal oxide, radionuclide. For example, U.S. Patent No. 4,673,562, to Davison et al. discloses representative chelating compounds and their synthesis.

T Cell Compositions

The present invention, in another aspect, provides T cells specific for a tumor polypeptide disclosed herein, or for a variant or derivative thereof. Such cells may generally be prepared *in vitro* or *ex vivo*, using standard procedures. For example, T cells may be isolated from bone marrow, peripheral blood, or a fraction of bone marrow or peripheral blood of a patient, using a commercially available cell separation system, such as the Isolex™ System, available from Nexell Therapeutics, Inc. (Irvine, CA; see also U.S. Patent No. 5,240,856; U.S. Patent No. 5,215,926; WO 89/06280; WO 91/16116 and WO 92/07243). Alternatively, T cells may be derived from related or unrelated humans, non-human mammals, cell lines or cultures.

T cells may be stimulated with a polypeptide, polynucleotide encoding a polypeptide and/or an antigen presenting cell (APC) that expresses such a polypeptide. Such stimulation is performed under conditions and for a time sufficient to permit the

generation of T cells that are specific for the polypeptide of interest. Preferably, a tumor polypeptide or polynucleotide of the invention is present within a delivery vehicle, such as a microsphere, to facilitate the generation of specific T cells.

T cells are considered to be specific for a polypeptide of the present invention if the T cells specifically proliferate, secrete cytokines or kill target cells coated with the polypeptide or expressing a gene encoding the polypeptide. T cell specificity may be evaluated using any of a variety of standard techniques. For example, within a chromium release assay or proliferation assay, a stimulation index of more than two fold increase in lysis and/or proliferation, compared to negative controls, indicates T cell specificity. Such assays may be performed, for example, as described in Chen et al., *Cancer Res.* *54*:1065-1070, 1994. Alternatively, detection of the proliferation of T cells may be accomplished by a variety of known techniques. For example, T cell proliferation can be detected by measuring an increased rate of DNA synthesis (*e.g.*, by pulse-labeling cultures of T cells with tritiated thymidine and measuring the amount of tritiated thymidine incorporated into DNA). Contact with a tumor polypeptide (100 ng/ml - 100 μg/ml, preferably 200 ng/ml - 25 μg/ml) for 3 - 7 days will typically result in at least a two fold increase in proliferation of the T cells. Contact as described above for 2-3 hours should result in activation of the T cells, as measured using standard cytokine assays in which a two fold increase in the level of cytokine release (*e.g.*, TNF or IFN-γ) is indicative of T cell activation (*see* Coligan et al., Current Protocols in Immunology, vol. 1, Wiley Interscience (Greene 1998)). T cells that have been activated in response to a tumor polypeptide, polynucleotide or polypeptide-expressing APC may be $CD4^+$ and/or $CD8^+$. Tumor polypeptide-specific T cells may be expanded using standard techniques. Within preferred embodiments, the T cells are derived from a patient, a related donor or an unrelated donor, and are administered to the patient following stimulation and expansion.

For therapeutic purposes, $CD4^+$ or $CD8^+$ T cells that proliferate in response to a tumor polypeptide, polynucleotide or APC can be expanded in number either *in vitro* or *in vivo*. Proliferation of such T cells *in vitro* may be accomplished in a variety of ways. For example, the T cells can be re-exposed to a tumor polypeptide, or a short peptide corresponding to an immunogenic portion of such a polypeptide, with or without the addition of T cell growth factors, such as interleukin-2, and/or stimulator

cells that synthesize a tumor polypeptide. Alternatively, one or more T cells that proliferate in the presence of the tumor polypeptide can be expanded in number by cloning. Methods for cloning cells are well known in the art, and include limiting dilution.

Pharmaceutical Compositions

In additional embodiments, the present invention concerns formulation of one or more of the polynucleotide, polypeptide, T-cell and/or antibody compositions disclosed herein in pharmaceutically-acceptable carriers for administration to a cell or an animal, either alone, or in combination with one or more other modalities of therapy.

It will be understood that, if desired, a composition as disclosed herein may be administered in combination with other agents as well, such as, *e.g.*, other proteins or polypeptides or various pharmaceutically-active agents. In fact, there is virtually no limit to other components that may also be included, given that the additional agents do not cause a significant adverse effect upon contact with the target cells or host tissues. The compositions may thus be delivered along with various other agents as required in the particular instance. Such compositions may be purified from host cells or other biological sources, or alternatively may be chemically synthesized as described herein. Likewise, such compositions may further comprise substituted or derivatized RNA or DNA compositions.

Therefore, in another aspect of the present invention, pharmaceutical compositions are provided comprising one or more of the polynucleotide, polypeptide, antibody, and/or T-cell compositions described herein in combination with a physiologically acceptable carrier. In certain preferred embodiments, the pharmaceutical compositions of the invention comprise immunogenic polynucleotide and/or polypeptide compositions of the invention for use in prophylactic and theraputic vaccine applications. Vaccine preparation is generally described in, for example, M.F. Powell and M.J. Newman, eds., "Vaccine Design (the subunit and adjuvant approach)," Plenum Press (NY, 1995). Generally, such compositions will comprise one or more polynucleotide and/or polypeptide compositions of the present invention in combination with one or more immunostimulants.

It will be apparent that any of the pharmaceutical compositions described herein can contain pharmaceutically acceptable salts of the polynucleotides and polypeptides of the invention. Such salts can be prepared, for example, from pharmaceutically acceptable non-toxic bases, including organic bases (*e.g.*, salts of primary, secondary and tertiary amines and basic amino acids) and inorganic bases (*e.g.*, sodium, potassium, lithium, ammonium, calcium and magnesium salts).

In another embodiment, illustrative immunogenic compositions, *e.g.*, vaccine compositions, of the present invention comprise DNA encoding one or more of the polypeptides as described above, such that the polypeptide is generated *in situ*. As noted above, the polynucleotide may be administered within any of a variety of delivery systems known to those of ordinary skill in the art. Indeed, numerous gene delivery techniques are well known in the art, such as those described by Rolland, *Crit. Rev. Therap. Drug Carrier Systems 15*:143-198, 1998, and references cited therein. Appropriate polynucleotide expression systems will, of course, contain the necessary regulatory DNA regulatory sequences for expression in a patient (such as a suitable promoter and terminating signal). Alternatively, bacterial delivery systems may involve the administration of a bacterium (such as *Bacillus-Calmette-Guerrin*) that expresses an immunogenic portion of the polypeptide on its cell surface or secretes such an epitope.

Therefore, in certain embodiments, polynucleotides encoding immunogenic polypeptides described herein are introduced into suitable mammalian host cells for expression using any of a number of known viral-based systems. In one illustrative embodiment, retroviruses provide a convenient and effective platform for gene delivery systems. A selected nucleotide sequence encoding a polypeptide of the present invention can be inserted into a vector and packaged in retroviral particles using techniques known in the art. The recombinant virus can then be isolated and delivered to a subject. A number of illustrative retroviral systems have been described (*e.g.*, U.S. Pat. No. 5,219,740; Miller and Rosman (1989) BioTechniques 7:980-990; Miller, A. D. (1990) Human Gene Therapy 1:5-14; Scarpa et al. (1991) Virology 180:849-852; Burns et al. (1993) Proc. Natl. Acad. Sci. USA 90:8033-8037; and Boris-Lawrie and Temin (1993) Cur. Opin. Genet. Develop. 3:102-109.

In addition, a number of illustrative adenovirus-based systems have also been described. Unlike retroviruses which integrate into the host genome, adenoviruses

persist extrachromosomally thus minimizing the risks associated with insertional mutagenesis (Haj-Ahmad and Graham (1986) J. Virol. 57:267-274; Bett et al. (1993) J. Virol. 67:5911-5921; Mittereder et al. (1994) Human Gene Therapy 5:717-729; Seth et al. (1994) J. Virol. 68:933-940; Barr et al. (1994) Gene Therapy 1:51-58; Berkner, K. L. (1988) BioTechniques 6:616-629; and Rich et al. (1993) Human Gene Therapy 4:461-476).

Various adeno-associated virus (AAV) vector systems have also been developed for polynucleotide delivery. AAV vectors can be readily constructed using techniques well known in the art. See, *e.g.*, U.S. Pat. Nos. 5,173,414 and 5,139,941; International Publication Nos. WO 92/01070 and WO 93/03769; Lebkowski et al. (1988) Molec. Cell. Biol. 8:3988-3996; Vincent et al. (1990) Vaccines 90 (Cold Spring Harbor Laboratory Press); Carter, B. J. (1992) Current Opinion in Biotechnology 3:533-539; Muzyczka, N. (1992) Current Topics in Microbiol. and Immunol. 158:97-129; Kotin, R. M. (1994) Human Gene Therapy 5:793-801; Shelling and Smith (1994) Gene Therapy 1:165-169; and Zhou et al. (1994) J. Exp. Med. 179:1867-1875.

Additional viral vectors useful for delivering the polynucleotides encoding polypeptides of the present invention by gene transfer include those derived from the pox family of viruses, such as vaccinia virus and avian poxvirus. By way of example, vaccinia virus recombinants expressing the novel molecules can be constructed as follows. The DNA encoding a polypeptide is first inserted into an appropriate vector so that it is adjacent to a vaccinia promoter and flanking vaccinia DNA sequences, such as the sequence encoding thymidine kinase (TK). This vector is then used to transfect cells which are simultaneously infected with vaccinia. Homologous recombination serves to insert the vaccinia promoter plus the gene encoding the polypeptide of interest into the viral genome. The resulting TK.sup.(-) recombinant can be selected by culturing the cells in the presence of 5-bromodeoxyuridine and picking viral plaques resistant thereto.

A vaccinia-based infection/transfection system can be conveniently used to provide for inducible, transient expression or coexpression of one or more polypeptides described herein in host cells of an organism. In this particular system, cells are first infected in vitro with a vaccinia virus recombinant that encodes the bacteriophage T7 RNA polymerase. This polymerase displays exquisite specificity in

that it only transcribes templates bearing T7 promoters. Following infection, cells are transfected with the polynucleotide or polynucleotides of interest, driven by a T7 promoter. The polymerase expressed in the cytoplasm from the vaccinia virus recombinant transcribes the transfected DNA into RNA which is then translated into polypeptide by the host translational machinery. The method provides for high level, transient, cytoplasmic production of large quantities of RNA and its translation products. See, *e.g.*, Elroy-Stein and Moss, Proc. Natl. Acad. Sci. USA (1990) 87:6743-6747; Fuerst et al. Proc. Natl. Acad. Sci. USA (1986) 83:8122-8126.

Alternatively, avipoxviruses, such as the fowlpox and canarypox viruses, can also be used to deliver the coding sequences of interest. Recombinant avipox viruses, expressing immunogens from mammalian pathogens, are known to confer protective immunity when administered to non-avian species. The use of an Avipox vector is particularly desirable in human and other mammalian species since members of the Avipox genus can only productively replicate in susceptible avian species and therefore are not infective in mammalian cells. Methods for producing recombinant Avipoxviruses are known in the art and employ genetic recombination, as described above with respect to the production of vaccinia viruses. See, *e.g.*, WO 91/12882; WO 89/03429; and WO 92/03545.

Any of a number of alphavirus vectors can also be used for delivery of polynucleotide compositions of the present invention, such as those vectors described in U.S. Patent Nos. 5,843,723; 6,015,686; 6,008,035 and 6,015,694. Certain vectors based on Venezuelan Equine Encephalitis (VEE) can also be used, illustrative examples of which can be found in U.S. Patent Nos. 5,505,947 and 5,643,576.

Moreover, molecular conjugate vectors, such as the adenovirus chimeric vectors described in Michael et al. J. Biol. Chem. (1993) 268:6866-6869 and Wagner et al. Proc. Natl. Acad. Sci. USA (1992) 89:6099-6103, can also be used for gene delivery under the invention.

Additional illustrative information on these and other known viral-based delivery systems can be found, for example, in Fisher-Hoch et al., *Proc. Natl. Acad. Sci. USA 86*:317-321, 1989; Flexner et al., *Ann. N.Y. Acad. Sci. 569*:86-103, 1989; Flexner et al., *Vaccine 8*:17-21, 1990; U.S. Patent Nos. 4,603,112, 4,769,330, and 5,017,487; WO 89/01973; U.S. Patent No. 4,777,127; GB 2,200,651; EP 0,345,242;

WO 91/02805; Berkner, *Biotechniques 6*:616-627, 1988; Rosenfeld et al., *Science 252*:431-434, 1991; Kolls et al., *Proc. Natl. Acad. Sci. USA 91*:215-219, 1994; Kass-Eisler et al., *Proc. Natl. Acad. Sci. USA 90*:11498-11502, 1993; Guzman et al., *Circulation 88*:2838-2848, 1993; and Guzman et al., *Cir. Res. 73*:1202-1207, 1993.

In certain embodiments, a polynucleotide may be integrated into the genome of a target cell. This integration may be in the specific location and orientation *via* homologous recombination (gene replacement) or it may be integrated in a random, non-specific location (gene augmentation). In yet further embodiments, the polynucleotide may be stably maintained in the cell as a separate, episomal segment of DNA. Such polynucleotide segments or "episomes" encode sequences sufficient to permit maintenance and replication independent of or in synchronization with the host cell cycle. The manner in which the expression construct is delivered to a cell and where in the cell the polynucleotide remains is dependent on the type of expression construct employed.

In another embodiment of the invention, a polynucleotide is administered/delivered as "naked" DNA, for example as described in Ulmer et al., *Science 259*:1745-1749, 1993 and reviewed by Cohen, *Science 259*:1691-1692, 1993. The uptake of naked DNA may be increased by coating the DNA onto biodegradable beads, which are efficiently transported into the cells.

In still another embodiment, a composition of the present invention can be delivered via a particle bombardment approach, many of which have been described. In one illustrative example, gas-driven particle acceleration can be achieved with devices such as those manufactured by Powderject Pharmaceuticals PLC (Oxford, UK) and Powderject Vaccines Inc. (Madison, WI), some examples of which are described in U.S. Patent Nos. 5,846,796; 6,010,478; 5,865,796; 5,584,807; and EP Patent No. 0500 799. This approach offers a needle-free delivery approach wherein a dry powder formulation of microscopic particles, such as polynucleotide or polypeptide particles, are accelerated to high speed within a helium gas jet generated by a hand held device, propelling the particles into a target tissue of interest.

In a related embodiment, other devices and methods that may be useful for gas-driven needle-less injection of compositions of the present invention include those provided by Bioject, Inc. (Portland, OR), some examples of which are described

in U.S. Patent Nos. 4,790,824; 5,064,413; 5,312,335; 5,383,851; 5,399,163; 5,520,639 and 5,993,412.

According to another embodiment, the pharmaceutical compositions described herein will comprise one or more immunostimulants in addition to the immunogenic polynucleotide, polypeptide, antibody, T-cell and/or APC compositions of this invention. An immunostimulant refers to essentially any substance that enhances or potentiates an immune response (antibody and/or cell-mediated) to an exogenous antigen. One preferred type of immunostimulant comprises an adjuvant. Many adjuvants contain a substance designed to protect the antigen from rapid catabolism, such as aluminum hydroxide or mineral oil, and a stimulator of immune responses, such as lipid A, *Bortadella pertussis* or *Mycobacterium tuberculosis* derived proteins. Certain adjuvants are commercially available as, for example, Freund's Incomplete Adjuvant and Complete Adjuvant (Difco Laboratories, Detroit, MI); Merck Adjuvant 65 (Merck and Company, Inc., Rahway, NJ); AS-2 (SmithKline Beecham, Philadelphia, PA); aluminum salts such as aluminum hydroxide gel (alum) or aluminum phosphate; salts of calcium, iron or zinc; an insoluble suspension of acylated tyrosine; acylated sugars; cationically or anionically derivatized polysaccharides; polyphosphazenes; biodegradable microspheres; monophosphoryl lipid A and quil A. Cytokines, such as GM-CSF, interleukin-2, -7, -12, and other like growth factors, may also be used as adjuvants.

Within certain embodiments of the invention, the adjuvant composition is preferably one that induces an immune response predominantly of the Th1 type. High levels of Th1-type cytokines (*e.g.*, IFN-γ, TNFα, IL-2 and IL-12) tend to favor the induction of cell mediated immune responses to an administered antigen. In contrast, high levels of Th2-type cytokines (*e.g.*, IL-4, IL-5, IL-6 and IL-10) tend to favor the induction of humoral immune responses. Following application of a vaccine as provided herein, a patient will support an immune response that includes Th1- and Th2-type responses. Within a preferred embodiment, in which a response is predominantly Th1-type, the level of Th1-type cytokines will increase to a greater extent than the level of Th2-type cytokines. The levels of these cytokines may be readily assessed using standard assays. For a review of the families of cytokines, see Mosmann and Coffman, *Ann. Rev. Immunol.* 7:145-173, 1989.

Certain preferred adjuvants for eliciting a predominantly Th1-type response include, for example, a combination of monophosphoryl lipid A, preferably 3-de-O-acylated monophosphoryl lipid A, together with an aluminum salt. MPL® adjuvants are available from Corixa Corporation (Seattle, WA; *see*, for example, US Patent Nos. 4,436,727; 4,877,611; 4,866,034 and 4,912,094). CpG-containing oligonucleotides (in which the CpG dinucleotide is unmethylated) also induce a predominantly Th1 response. Such oligonucleotides are well known and are described, for example, in WO 96/02555, WO 99/33488 and U.S. Patent Nos. 6,008,200 and 5,856,462. Immunostimulatory DNA sequences are also described, for example, by Sato et al., *Science 273*:352, 1996. Another preferred adjuvant comprises a saponin, such as Quil A, or derivatives thereof, including QS21 and QS7 (Aquila Biopharmaceuticals Inc., Framingham, MA); Escin; Digitonin; or *Gypsophila* or *Chenopodium quinoa* saponins . Other preferred formulations include more than one saponin in the adjuvant combinations of the present invention, for example combinations of at least two of the following group comprising QS21, QS7, Quil A, β-escin, or digitonin.

Alternatively the saponin formulations may be combined with vaccine vehicles composed of chitosan or other polycationic polymers, polylactide and polylactide-co-glycolide particles, poly-N-acetyl glucosamine-based polymer matrix, particles composed of polysaccharides or chemically modified polysaccharides, liposomes and lipid-based particles, particles composed of glycerol monoesters, etc. The saponins may also be formulated in the presence of cholesterol to form particulate structures such as liposomes or ISCOMs. Furthermore, the saponins may be formulated together with a polyoxyethylene ether or ester, in either a non-particulate solution or suspension, or in a particulate structure such as a paucilamelar liposome or ISCOM. The saponins may also be formulated with excipients such as Carbopol^R to increase viscosity, or may be formulated in a dry powder form with a powder excipient such as lactose.

In one preferred embodiment, the adjuvant system includes the combination of a monophosphoryl lipid A and a saponin derivative, such as the combination of QS21 and 3D-MPL® adjuvant, as described in WO 94/00153, or a less reactogenic composition where the QS21 is quenched with cholesterol, as described in

WO 96/33739. Other preferred formulations comprise an oil-in-water emulsion and tocopherol. Another particularly preferred adjuvant formulation employing QS21, 3D-MPL® adjuvant and tocopherol in an oil-in-water emulsion is described in WO 95/17210.

Another enhanced adjuvant system involves the combination of a CpG-containing oligonucleotide and a saponin derivative particularly the combination of CpG and QS21 is disclosed in WO 00/09159. Preferably the formulation additionally comprises an oil in water emulsion and tocopherol.

Additional illustrative adjuvants for use in the pharmaceutical compositions of the invention include Montanide ISA 720 (Seppic, France), SAF (Chiron, California, United States), ISCOMS (CSL), MF-59 (Chiron), the SBAS series of adjuvants (*e.g.*, SBAS-2 or SBAS-4, available from SmithKline Beecham, Rixensart, Belgium), Detox (Enhanzyn®) (Corixa, Hamilton, MT), RC-529 (Corixa, Hamilton, MT) and other aminoalkyl glucosaminide 4-phosphates (AGPs), such as those described in pending U.S. Patent Application Serial Nos. 08/853,826 and 09/074,720, the disclosures of which are incorporated herein by reference in their entireties, and polyoxyethylene ether adjuvants such as those described in WO 99/52549A1.

Other preferred adjuvants include adjuvant molecules of the general formula

(I): $HO(CH_2CH_2O)_n$-A-R,

wherein, n is 1-50, A is a bond or –C(O)-, R is C_{1-50} alkyl or Phenyl C_{1-50} alkyl.

One embodiment of the present invention consists of a vaccine formulation comprising a polyoxyethylene ether of general formula (I), wherein *n* is between 1 and 50, preferably 4-24, most preferably 9; the *R* component is C_{1-50}, preferably C_4-C_{20} alkyl and most preferably C_{12} alkyl, and *A* is a bond. The concentration of the polyoxyethylene ethers should be in the range 0.1-20%, preferably from 0.1-10%, and most preferably in the range 0.1-1%. Preferred polyoxyethylene ethers are selected from the following group: polyoxyethylene-9-lauryl ether, polyoxyethylene-9-steoryl ether, polyoxyethylene-8-steoryl ether, polyoxyethylene-4-lauryl ether, polyoxyethylene-35-lauryl ether, and polyoxyethylene-23-lauryl ether. Polyoxyethylene ethers such as polyoxyethylene lauryl ether are described in the Merck

index (12th edition: entry 7717). These adjuvant molecules are described in WO 99/52549.

The polyoxyethylene ether according to the general formula (I) above may, if desired, be combined with another adjuvant. For example, a preferred adjuvant combination is preferably with CpG as described in the pending UK patent application GB 9820956.2.

According to another embodiment of this invention, an immunogenic composition described herein is delivered to a host via antigen presenting cells (APCs), such as dendritic cells, macrophages, B cells, monocytes and other cells that may be engineered to be efficient APCs. Such cells may, but need not, be genetically modified to increase the capacity for presenting the antigen, to improve activation and/or maintenance of the T cell response, to have anti-tumor effects *per se* and/or to be immunologically compatible with the receiver (*i.e.,* matched HLA haplotype). APCs may generally be isolated from any of a variety of biological fluids and organs, including tumor and peritumoral tissues, and may be autologous, allogeneic, syngeneic or xenogeneic cells.

Certain preferred embodiments of the present invention use dendritic cells or progenitors thereof as antigen-presenting cells. Dendritic cells are highly potent APCs (Banchereau and Steinman, *Nature 392*:245-251, 1998) and have been shown to be effective as a physiological adjuvant for eliciting prophylactic or therapeutic antitumor immunity (*see* Timmerman and Levy, *Ann. Rev. Med. 50*:507-529, 1999). In general, dendritic cells may be identified based on their typical shape (stellate *in situ*, with marked cytoplasmic processes (dendrites) visible *in vitro*), their ability to take up, process and present antigens with high efficiency and their ability to activate naïve T cell responses. Dendritic cells may, of course, be engineered to express specific cell-surface receptors or ligands that are not commonly found on dendritic cells *in vivo* or *ex vivo*, and such modified dendritic cells are contemplated by the present invention. As an alternative to dendritic cells, secreted vesicles antigen-loaded dendritic cells (called exosomes) may be used within a vaccine (*see* Zitvogel et al., *Nature Med. 4*:594-600, 1998).

Dendritic cells and progenitors may be obtained from peripheral blood, bone marrow, tumor-infiltrating cells, peritumoral tissues-infiltrating cells, lymph nodes, spleen, skin, umbilical cord blood or any other suitable tissue or fluid. For example, dendritic cells may be differentiated *ex vivo* by adding a combination of cytokines such as GM-CSF, IL-4, IL-13 and/or TNFα to cultures of monocytes harvested from peripheral blood. Alternatively, CD34 positive cells harvested from peripheral blood, umbilical cord blood or bone marrow may be differentiated into dendritic cells by adding to the culture medium combinations of GM-CSF, IL-3, TNFα, CD40 ligand, LPS, flt3 ligand and/or other compound(s) that induce differentiation, maturation and proliferation of dendritic cells.

Dendritic cells are conveniently categorized as "immature" and "mature" cells, which allows a simple way to discriminate between two well characterized phenotypes. However, this nomenclature should not be construed to exclude all possible intermediate stages of differentiation. Immature dendritic cells are characterized as APC with a high capacity for antigen uptake and processing, which correlates with the high expression of Fcγ receptor and mannose receptor. The mature phenotype is typically characterized by a lower expression of these markers, but a high expression of cell surface molecules responsible for T cell activation such as class I and class II MHC, adhesion molecules (*e.g.*, CD54 and CD11) and costimulatory molecules (*e.g.*, CD40, CD80, CD86 and 4-1BB).

APCs may generally be transfected with a polynucleotide of the invention (or portion or other variant thereof) such that the encoded polypeptide, or an immunogenic portion thereof, is expressed on the cell surface. Such transfection may take place *ex vivo*, and a pharmaceutical composition comprising such transfected cells may then be used for therapeutic purposes, as described herein. Alternatively, a gene delivery vehicle that targets a dendritic or other antigen presenting cell may be administered to a patient, resulting in transfection that occurs *in vivo*. *In vivo* and *ex vivo* transfection of dendritic cells, for example, may generally be performed using any methods known in the art, such as those described in WO 97/24447, or the gene gun approach described by Mahvi et al., *Immunology and cell Biology 75*:456-460, 1997. Antigen loading of dendritic cells may be achieved by incubating dendritic cells or progenitor cells with the tumor polypeptide, DNA (naked or within a plasmid vector) or

RNA; or with antigen-expressing recombinant bacterium or viruses (*e.g.*, vaccinia, fowlpox, adenovirus or lentivirus vectors). Prior to loading, the polypeptide may be covalently conjugated to an immunological partner that provides T cell help (*e.g.*, a carrier molecule). Alternatively, a dendritic cell may be pulsed with a non-conjugated immunological partner, separately or in the presence of the polypeptide.

While any suitable carrier known to those of ordinary skill in the art may be employed in the pharmaceutical compositions of this invention, the type of carrier will typically vary depending on the mode of administration. Compositions of the present invention may be formulated for any appropriate manner of administration, including for example, topical, oral, nasal, mucosal, intravenous, intracranial, intraperitoneal, subcutaneous and intramuscular administration.

Carriers for use within such pharmaceutical compositions are biocompatible, and may also be biodegradable. In certain embodiments, the formulation preferably provides a relatively constant level of active component release. In other embodiments, however, a more rapid rate of release immediately upon administration may be desired. The formulation of such compositions is well within the level of ordinary skill in the art using known techniques. Illustrative carriers useful in this regard include microparticles of poly(lactide-co-glycolide), polyacrylate, latex, starch, cellulose, dextran and the like. Other illustrative delayed-release carriers include supramolecular biovectors, which comprise a non-liquid hydrophilic core (*e.g.*, a cross-linked polysaccharide or oligosaccharide) and, optionally, an external layer comprising an amphiphilic compound, such as a phospholipid (*see e.g.*, U.S. Patent No. 5,151,254 and PCT applications WO 94/20078, WO/94/23701 and WO 96/06638). The amount of active compound contained within a sustained release formulation depends upon the site of implantation, the rate and expected duration of release and the nature of the condition to be treated or prevented.

In another illustrative embodiment, biodegradable microspheres (*e.g.*, polylactate polyglycolate) are employed as carriers for the compositions of this invention. Suitable biodegradable microspheres are disclosed, for example, in U.S. Patent Nos. 4,897,268; 5,075,109; 5,928,647; 5,811,128; 5,820,883; 5,853,763; 5,814,344, 5,407,609 and 5,942,252. Modified hepatitis B core protein carrier systems. such as described in WO/99 40934, and references cited therein, will also be useful for

many applications. Another illustrative carrier/delivery system employs a carrier comprising particulate-protein complexes, such as those described in U.S. Patent No. 5,928,647, which are capable of inducing a class I-restricted cytotoxic T lymphocyte responses in a host.

The pharmaceutical compositions of the invention will often further comprise one or more buffers (*e.g.*, neutral buffered saline or phosphate buffered saline), carbohydrates (*e.g.*, glucose, mannose, sucrose or dextrans), mannitol, proteins, polypeptides or amino acids such as glycine, antioxidants, bacteriostats, chelating agents such as EDTA or glutathione, adjuvants (*e.g.*, aluminum hydroxide), solutes that render the formulation isotonic, hypotonic or weakly hypertonic with the blood of a recipient, suspending agents, thickening agents and/or preservatives. Alternatively, compositions of the present invention may be formulated as a lyophilizate.

The pharmaceutical compositions described herein may be presented in unit-dose or multi-dose containers, such as sealed ampoules or vials. Such containers are typically sealed in such a way to preserve the sterility and stability of the formulation until use. In general, formulations may be stored as suspensions, solutions or emulsions in oily or aqueous vehicles. Alternatively, a pharmaceutical composition may be stored in a freeze-dried condition requiring only the addition of a sterile liquid carrier immediately prior to use.

The development of suitable dosing and treatment regimens for using the particular compositions described herein in a variety of treatment regimens, including *e.g.*, oral, parenteral, intravenous, intranasal, and intramuscular administration and formulation, is well known in the art, some of which are briefly discussed below for general purposes of illustration.

In certain applications, the pharmaceutical compositions disclosed herein may be delivered *via* oral administration to an animal. As such, these compositions may be formulated with an inert diluent or with an assimilable edible carrier, or they may be enclosed in hard- or soft-shell gelatin capsule, or they may be compressed into tablets, or they may be incorporated directly with the food of the diet.

The active compounds may even be incorporated with excipients and used in the form of ingestible tablets, buccal tables, troches, capsules, elixirs, suspensions, syrups, wafers, and the like (see, for example, Mathiowitz *et al.*, Nature

1997 Mar 27;386(6623):410-4; Hwang *et al.*, Crit Rev Ther Drug Carrier Syst 1998;15(3):243-84; U. S. Patent 5,641,515; U. S. Patent 5,580,579 and U. S. Patent 5,792,451). Tablets, troches, pills, capsules and the like may also contain any of a variety of additional components, for example, a binder, such as gum tragacanth, acacia, cornstarch, or gelatin; excipients, such as dicalcium phosphate; a disintegrating agent, such as corn starch, potato starch, alginic acid and the like; a lubricant, such as magnesium stearate; and a sweetening agent, such as sucrose, lactose or saccharin may be added or a flavoring agent, such as peppermint, oil of wintergreen, or cherry flavoring. When the dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets, pills, or capsules may be coated with shellac, sugar, or both. Of course, any material used in preparing any dosage unit form should be pharmaceutically pure and substantially non-toxic in the amounts employed. In addition, the active compounds may be incorporated into sustained-release preparation and formulations.

Typically, these formulations will contain at least about 0.1% of the active compound or more, although the percentage of the active ingredient(s) may, of course, be varied and may conveniently be between about 1 or 2% and about 60% or 70% or more of the weight or volume of the total formulation. Naturally, the amount of active compound(s) in each therapeutically useful composition may be prepared is such a way that a suitable dosage will be obtained in any given unit dose of the compound. Factors such as solubility, bioavailability, biological half-life, route of administration, product shelf life, as well as other pharmacological considerations will be contemplated by one skilled in the art of preparing such pharmaceutical formulations, and as such, a variety of dosages and treatment regimens may be desirable.

For oral administration the compositions of the present invention may alternatively be incorporated with one or more excipients in the form of a mouthwash, dentifrice, buccal tablet, oral spray, or sublingual orally-administered formulation. Alternatively, the active ingredient may be incorporated into an oral solution such as one containing sodium borate, glycerin and potassium bicarbonate, or dispersed in a dentifrice, or added in a therapeutically-effective amount to a composition that may include water, binders, abrasives, flavoring agents, foaming agents, and humectants.

Alternatively the compositions may be fashioned into a tablet or solution form that may be placed under the tongue or otherwise dissolved in the mouth.

In certain circumstances it will be desirable to deliver the pharmaceutical compositions disclosed herein parenterally, intravenously, intramuscularly, or even intraperitoneally. Such approaches are well known to the skilled artisan, some of which are further described, for example, in U. S. Patent 5,543,158; U. S. Patent 5,641,515 and U. S. Patent 5,399,363. In certain embodiments, solutions of the active compounds as free base or pharmacologically acceptable salts may be prepared in water suitably mixed with a surfactant, such as hydroxypropylcellulose. Dispersions may also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations generally will contain a preservative to prevent the growth of microorganisms.

Illustrative pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions (for example, see U. S. Patent 5,466,468). In all cases the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms, such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (*e.g.*, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), suitable mixtures thereof, and/or vegetable oils. Proper fluidity may be maintained, for example, by the use of a coating, such as lecithin, by the maintenance of the required particle size in the case of dispersion and/or by the use of surfactants. The prevention of the action of microorganisms can be facilitated by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

In one embodiment, for parenteral administration in an aqueous solution, the solution should be suitably buffered if necessary and the liquid diluent first rendered

isotonic with sufficient saline or glucose. These particular aqueous solutions are especially suitable for intravenous, intramuscular, subcutaneous and intraperitoneal administration. In this connection, a sterile aqueous medium that can be employed will be known to those of skill in the art in light of the present disclosure. For example, one dosage may be dissolved in 1 ml of isotonic NaCl solution and either added to 1000 ml of hypodermoclysis fluid or injected at the proposed site of infusion, (see for example, "Remington's Pharmaceutical Sciences" 15th Edition, pages 1035-1038 and 1570-1580). Some variation in dosage will necessarily occur depending on the condition of the subject being treated. Moreover, for human administration, preparations will of course preferably meet sterility, pyrogenicity, and the general safety and purity standards as required by FDA Office of Biologics standards.

In another embodiment of the invention, the compositions disclosed herein may be formulated in a neutral or salt form. Illustrative pharmaceutically-acceptable salts include the acid addition salts (formed with the free amino groups of the protein) and which are formed with inorganic acids such as, for example, hydrochloric or phosphoric acids, or such organic acids as acetic, oxalic, tartaric, mandelic, and the like. Salts formed with the free carboxyl groups can also be derived from inorganic bases such as, for example, sodium, potassium, ammonium, calcium, or ferric hydroxides, and such organic bases as isopropylamine, trimethylamine, histidine, procaine and the like. Upon formulation, solutions will be administered in a manner compatible with the dosage formulation and in such amount as is therapeutically effective.

The carriers can further comprise any and all solvents, dispersion media, vehicles, coatings, diluents, antibacterial and antifungal agents, isotonic and absorption delaying agents, buffers, carrier solutions, suspensions, colloids, and the like. The use of such media and agents for pharmaceutical active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic compositions is contemplated. Supplementary active ingredients can also be incorporated into the compositions. The phrase "pharmaceutically-acceptable" refers to molecular entities and compositions that do not produce an allergic or similar untoward reaction when administered to a human.

In certain embodiments, the pharmaceutical compositions may be delivered by intranasal sprays, inhalation, and/or other aerosol delivery vehicles. Methods for delivering genes, nucleic acids, and peptide compositions directly to the lungs *via* nasal aerosol sprays has been described, *e.g.,* in U. S. Patent 5,756,353 and U. S. Patent 5,804,212. Likewise, the delivery of drugs using intranasal microparticle resins (Takenaga *et al.*, J Controlled Release 1998 Mar 2;52(1-2):81-7) and lysophosphatidyl-glycerol compounds (U. S. Patent 5,725,871) are also well-known in the pharmaceutical arts. Likewise, illustrative transmucosal drug delivery in the form of a polytetrafluoroetheylene support matrix is described in U. S. Patent 5,780,045.

In certain embodiments, liposomes, nanocapsules, microparticles, lipid particles, vesicles, and the like, are used for the introduction of the compositions of the present invention into suitable host cells/organisms. In particular, the compositions of the present invention may be formulated for delivery either encapsulated in a lipid particle, a liposome, a vesicle, a nanosphere, or a nanoparticle or the like. Alternatively, compositions of the present invention can be bound, either covalently or non-covalently, to the surface of such carrier vehicles.

The formation and use of liposome and liposome-like preparations as potential drug carriers is generally known to those of skill in the art (see for example, Lasic, Trends Biotechnol 1998 Jul;16(7):307-21; Takakura, Nippon Rinsho 1998 Mar;56(3):691-5; Chandran *et al.*, Indian J Exp Biol. 1997 Aug;35(8):801-9; Margalit, Crit Rev Ther Drug Carrier Syst. 1995;12(2-3):233-61; U.S. Patent 5,567,434; U.S. Patent 5,552,157; U.S. Patent 5,565,213; U.S. Patent 5,738,868 and U.S. Patent 5,795,587, each specifically incorporated herein by reference in its entirety).

Liposomes have been used successfully with a number of cell types that are normally difficult to transfect by other procedures, including T cell suspensions, primary hepatocyte cultures and PC 12 cells (Renneisen *et al.,* J Biol Chem. 1990 Sep 25;265(27):16337-42; Muller *et al.*, DNA Cell Biol. 1990 Apr;9(3):221-9). In addition, liposomes are free of the DNA length constraints that are typical of viral-based delivery systems. Liposomes have been used effectively to introduce genes, various drugs, radiotherapeutic agents, enzymes, viruses, transcription factors, allosteric effectors and the like, into a variety of cultured cell lines and animals. Furthermore, he use of

liposomes does not appear to be associated with autoimmune responses or unacceptable toxicity after systemic delivery.

In certain embodiments, liposomes are formed from phospholipids that are dispersed in an aqueous medium and spontaneously form multilamellar concentric bilayer vesicles (also termed multilamellar vesicles (MLVs).

Alternatively, in other embodiments, the invention provides for pharmaceutically-acceptable nanocapsule formulations of the compositions of the present invention. Nanocapsules can generally entrap compounds in a stable and reproducible way (see, for example, Quintanar-Guerrero *et al.*, Drug Dev Ind Pharm. 1998 Dec;24(12):1113-28). To avoid side effects due to intracellular polymeric overloading, such ultrafine particles (sized around 0.1 μm) may be designed using polymers able to be degraded *in vivo*. Such particles can be made as described, for example, by Couvreur *et al.*, Crit Rev Ther Drug Carrier Syst. 1988;5(1):1-20; zur Muhlen *et al.*, Eur J Pharm Biopharm. 1998 Mar;45(2):149-55; Zambaux *et al.* J Controlled Release. 1998 Jan 2;50(1-3):31-40; and U. S. Patent 5,145,684.

Cancer Therapeutic Methods

In further aspects of the present invention, the pharmaceutical compositions described herein may be used for the treatment of cancer, particularly for the immunotherapy of lung cancer. Within such methods, the pharmaceutical compositions described herein are administered to a patient, typically a warm-blooded animal, preferably a human. A patient may or may not be afflicted with cancer. Accordingly, the above pharmaceutical compositions may be used to prevent the development of a cancer or to treat a patient afflicted with a cancer. Pharmaceutical compositions and vaccines may be administered either prior to or following surgical removal of primary tumors and/or treatment such as administration of radiotherapy or conventional chemotherapeutic drugs. As discussed above, administration of the pharmaceutical compositions may be by any suitable method, including administration by intravenous, intraperitoneal, intramuscular, subcutaneous, intranasal, intradermal, anal, vaginal, topical and oral routes.

Within certain embodiments, immunotherapy may be active immunotherapy, in which treatment relies on the *in vivo* stimulation of the endogenous

host immune system to react against tumors with the administration of immune response-modifying agents (such as polypeptides and polynucleotides as provided herein).

Within other embodiments, immunotherapy may be passive immunotherapy, in which treatment involves the delivery of agents with established tumor-immune reactivity (such as effector cells or antibodies) that can directly or indirectly mediate antitumor effects and does not necessarily depend on an intact host immune system. Examples of effector cells include T cells as discussed above, T lymphocytes (such as $CD8^+$ cytotoxic T lymphocytes and $CD4^+$ T-helper tumor-infiltrating lymphocytes), killer cells (such as Natural Killer cells and lymphokine-activated killer cells), B cells and antigen-presenting cells (such as dendritic cells and macrophages) expressing a polypeptide provided herein. T cell receptors and antibody receptors specific for the polypeptides recited herein may be cloned, expressed and transferred into other vectors or effector cells for adoptive immunotherapy. The polypeptides provided herein may also be used to generate antibodies or anti-idiotypic antibodies (as described above and in U.S. Patent No. 4,918,164) for passive immunotherapy.

Effector cells may generally be obtained in sufficient quantities for adoptive immunotherapy by growth *in vitro*, as described herein. Culture conditions for expanding single antigen-specific effector cells to several billion in number with retention of antigen recognition *in vivo* are well known in the art. Such *in vitro* culture conditions typically use intermittent stimulation with antigen, often in the presence of cytokines (such as IL-2) and non-dividing feeder cells. As noted above, immunoreactive polypeptides as provided herein may be used to rapidly expand antigen-specific T cell cultures in order to generate a sufficient number of cells for immunotherapy. In particular, antigen-presenting cells, such as dendritic, macrophage, monocyte, fibroblast and/or B cells, may be pulsed with immunoreactive polypeptides or transfected with one or more polynucleotides using standard techniques well known in the art. For example, antigen-presenting cells can be transfected with a polynucleotide having a promoter appropriate for increasing expression in a recombinant virus or other expression system. Cultured effector cells for use in therapy must be able to grow and distribute widely, and to survive long term *in vivo*. Studies

have shown that cultured effector cells can be induced to grow in vivo and to survive long term in substantial numbers by repeated stimulation with antigen supplemented with IL-2 (*see*, for example, Cheever et al., *Immunological Reviews 157*:177, 1997).

Alternatively, a vector expressing a polypeptide recited herein may be introduced into antigen presenting cells taken from a patient and clonally propagated *ex vivo* for transplant back into the same patient. Transfected cells may be reintroduced into the patient using any means known in the art, preferably in sterile form by intravenous, intracavitary, intraperitoneal or intratumor administration.

Routes and frequency of administration of the therapeutic compositions described herein, as well as dosage, will vary from individual to individual, and may be readily established using standard techniques. In general, the pharmaceutical compositions and vaccines may be administered by injection (*e.g.*, intracutaneous, intramuscular, intravenous or subcutaneous), intranasally (*e.g.*, by aspiration) or orally. Preferably, between 1 and 10 doses may be administered over a 52 week period. Preferably, 6 doses are administered, at intervals of 1 month, and booster vaccinations may be given periodically thereafter. Alternate protocols may be appropriate for individual patients. A suitable dose is an amount of a compound that, when administered as described above, is capable of promoting an anti-tumor immune response, and is at least 10-50% above the basal (*i.e.*, untreated) level. Such response can be monitored by measuring the anti-tumor antibodies in a patient or by vaccine-dependent generation of cytolytic effector cells capable of killing the patient's tumor cells *in vitro*. Such vaccines should also be capable of causing an immune response that leads to an improved clinical outcome (*e.g.*, more frequent remissions, complete or partial or longer disease-free survival) in vaccinated patients as compared to non-vaccinated patients. In general, for pharmaceutical compositions and vaccines comprising one or more polypeptides, the amount of each polypeptide present in a dose ranges from about 25 µg to 5 mg per kg of host. Suitable dose sizes will vary with the size of the patient, but will typically range from about 0.1 mL to about 5 mL.

In general, an appropriate dosage and treatment regimen provides the active compound(s) in an amount sufficient to provide therapeutic and/or prophylactic benefit. Such a response can be monitored by establishing an improved clinical outcome (*e.g.*, more frequent remissions, complete or partial, or longer disease-free

survival) in treated patients as compared to non-treated patients. Increases in preexisting immune responses to a tumor protein generally correlate with an improved clinical outcome. Such immune responses may generally be evaluated using standard proliferation, cytotoxicity or cytokine assays, which may be performed using samples obtained from a patient before and after treatment.

Cancer Detection and Diagnostic Compositions, Methods and Kits

In general, a cancer may be detected in a patient based on the presence of one or more lung tumor proteins and/or polynucleotides encoding such proteins in a biological sample (for example, blood, sera, sputum urine and/or tumor biopsies) obtained from the patient. In other words, such proteins may be used as markers to indicate the presence or absence of a cancer such as lung cancer. In addition, such proteins may be useful for the detection of other cancers. The binding agents provided herein generally permit detection of the level of antigen that binds to the agent in the biological sample. Polynucleotide primers and probes may be used to detect the level of mRNA encoding a tumor protein, which is also indicative of the presence or absence of a cancer. In general, a lung tumor sequence should be present at a level that is at least three fold higher in tumor tissue than in normal tissue

There are a variety of assay formats known to those of ordinary skill in the art for using a binding agent to detect polypeptide markers in a sample. *See, e.g.*, Harlow and Lane, *Antibodies: A Laboratory Manual,* Cold Spring Harbor Laboratory, 1988. In general, the presence or absence of a cancer in a patient may be determined by (a) contacting a biological sample obtained from a patient with a binding agent; (b) detecting in the sample a level of polypeptide that binds to the binding agent; and (c) comparing the level of polypeptide with a predetermined cut-off value.

In a preferred embodiment, the assay involves the use of binding agent immobilized on a solid support to bind to and remove the polypeptide from the remainder of the sample. The bound polypeptide may then be detected using a detection reagent that contains a reporter group and specifically binds to the binding agent/polypeptide complex. Such detection reagents may comprise, for example, a binding agent that specifically binds to the polypeptide or an antibody or other agent that specifically binds to the binding agent, such as an anti-immunoglobulin, protein G,

protein A or a lectin. Alternatively, a competitive assay may be utilized, in which a polypeptide is labeled with a reporter group and allowed to bind to the immobilized binding agent after incubation of the binding agent with the sample. The extent to which components of the sample inhibit the binding of the labeled polypeptide to the binding agent is indicative of the reactivity of the sample with the immobilized binding agent. Suitable polypeptides for use within such assays include full length lung tumor proteins and polypeptide portions thereof to which the binding agent binds, as described above.

The solid support may be any material known to those of ordinary skill in the art to which the tumor protein may be attached. For example, the solid support may be a test well in a microtiter plate or a nitrocellulose or other suitable membrane. Alternatively, the support may be a bead or disc, such as glass, fiberglass, latex or a plastic material such as polystyrene or polyvinylchloride. The support may also be a magnetic particle or a fiber optic sensor, such as those disclosed, for example, in U.S. Patent No. 5,359,681. The binding agent may be immobilized on the solid support using a variety of techniques known to those of skill in the art, which are amply described in the patent and scientific literature. In the context of the present invention, the term "immobilization" refers to both noncovalent association, such as adsorption, and covalent attachment (which may be a direct linkage between the agent and functional groups on the support or may be a linkage by way of a cross-linking agent). Immobilization by adsorption to a well in a microtiter plate or to a membrane is preferred. In such cases, adsorption may be achieved by contacting the binding agent, in a suitable buffer, with the solid support for a suitable amount of time. The contact time varies with temperature, but is typically between about 1 hour and about 1 day. In general, contacting a well of a plastic microtiter plate (such as polystyrene or polyvinylchloride) with an amount of binding agent ranging from about 10 ng to about 10 µg, and preferably about 100 ng to about 1 µg, is sufficient to immobilize an adequate amount of binding agent.

Covalent attachment of binding agent to a solid support may generally be achieved by first reacting the support with a bifunctional reagent that will react with both the support and a functional group, such as a hydroxyl or amino group, on the binding agent. For example, the binding agent may be covalently attached to supports

having an appropriate polymer coating using benzoquinone or by condensation of an aldehyde group on the support with an amine and an active hydrogen on the binding partner (*see, e.g.*, Pierce Immunotechnology Catalog and Handbook, 1991, at A12-A13).

In certain embodiments, the assay is a two-antibody sandwich assay. This assay may be performed by first contacting an antibody that has been immobilized on a solid support, commonly the well of a microtiter plate, with the sample, such that polypeptides within the sample are allowed to bind to the immobilized antibody. Unbound sample is then removed from the immobilized polypeptide-antibody complexes and a detection reagent (preferably a second antibody capable of binding to a different site on the polypeptide) containing a reporter group is added. The amount of detection reagent that remains bound to the solid support is then determined using a method appropriate for the specific reporter group.

More specifically, once the antibody is immobilized on the support as described above, the remaining protein binding sites on the support are typically blocked. Any suitable blocking agent known to those of ordinary skill in the art, such as bovine serum albumin or Tween 20™ (Sigma Chemical Co., St. Louis, MO). The immobilized antibody is then incubated with the sample, and polypeptide is allowed to bind to the antibody. The sample may be diluted with a suitable diluent, such as phosphate-buffered saline (PBS) prior to incubation. In general, an appropriate contact time (*i.e.*, incubation time) is a period of time that is sufficient to detect the presence of polypeptide within a sample obtained from an individual with lung cancer. Preferably, the contact time is sufficient to achieve a level of binding that is at least about 95% of that achieved at equilibrium between bound and unbound polypeptide. Those of ordinary skill in the art will recognize that the time necessary to achieve equilibrium may be readily determined by assaying the level of binding that occurs over a period of time. At room temperature, an incubation time of about 30 minutes is generally sufficient.

Unbound sample may then be removed by washing the solid support with an appropriate buffer, such as PBS containing 0.1% Tween 20™. The second antibody, which contains a reporter group, may then be added to the solid support. Preferred reporter groups include those groups recited above.

The detection reagent is then incubated with the immobilized antibody-polypeptide complex for an amount of time sufficient to detect the bound polypeptide. An appropriate amount of time may generally be determined by assaying the level of binding that occurs over a period of time. Unbound detection reagent is then removed and bound detection reagent is detected using the reporter group. The method employed for detecting the reporter group depends upon the nature of the reporter group. For radioactive groups, scintillation counting or autoradiographic methods are generally appropriate. Spectroscopic methods may be used to detect dyes, luminescent groups and fluorescent groups. Biotin may be detected using avidin, coupled to a different reporter group (commonly a radioactive or fluorescent group or an enzyme). Enzyme reporter groups may generally be detected by the addition of substrate (generally for a specific period of time), followed by spectroscopic or other analysis of the reaction products.

To determine the presence or absence of a cancer, such as lung cancer, the signal detected from the reporter group that remains bound to the solid support is generally compared to a signal that corresponds to a predetermined cut-off value. In one preferred embodiment, the cut-off value for the detection of a cancer is the average mean signal obtained when the immobilized antibody is incubated with samples from patients without the cancer. In general, a sample generating a signal that is three standard deviations above the predetermined cut-off value is considered positive for the cancer. In an alternate preferred embodiment, the cut-off value is determined using a Receiver Operator Curve, according to the method of Sackett et al., *Clinical Epidemiology: A Basic Science for Clinical Medicine*, Little Brown and Co., 1985, p. 106-7. Briefly, in this embodiment, the cut-off value may be determined from a plot of pairs of true positive rates (*i.e.*, sensitivity) and false positive rates (100%-specificity) that correspond to each possible cut-off value for the diagnostic test result. The cut-off value on the plot that is the closest to the upper left-hand corner (*i.e.*, the value that encloses the largest area) is the most accurate cut-off value, and a sample generating a signal that is higher than the cut-off value determined by this method may be considered positive. Alternatively, the cut-off value may be shifted to the left along the plot, to minimize the false positive rate, or to the right, to minimize the false negative rate. In

general, a sample generating a signal that is higher than the cut-off value determined by this method is considered positive for a cancer.

In a related embodiment, the assay is performed in a flow-through or strip test format, wherein the binding agent is immobilized on a membrane, such as nitrocellulose. In the flow-through test, polypeptides within the sample bind to the immobilized binding agent as the sample passes through the membrane. A second, labeled binding agent then binds to the binding agent-polypeptide complex as a solution containing the second binding agent flows through the membrane. The detection of bound second binding agent may then be performed as described above. In the strip test format, one end of the membrane to which binding agent is bound is immersed in a solution containing the sample. The sample migrates along the membrane through a region containing second binding agent and to the area of immobilized binding agent. Concentration of second binding agent at the area of immobilized antibody indicates the presence of a cancer. Typically, the concentration of second binding agent at that site generates a pattern, such as a line, that can be read visually. The absence of such a pattern indicates a negative result. In general, the amount of binding agent immobilized on the membrane is selected to generate a visually discernible pattern when the biological sample contains a level of polypeptide that would be sufficient to generate a positive signal in the two-antibody sandwich assay, in the format discussed above. Preferred binding agents for use in such assays are antibodies and antigen-binding fragments thereof. Preferably, the amount of antibody immobilized on the membrane ranges from about 25 ng to about 1μg, and more preferably from about 50 ng to about 500 ng. Such tests can typically be performed with a very small amount of biological sample.

Of course, numerous other assay protocols exist that are suitable for use with the tumor proteins or binding agents of the present invention. The above descriptions are intended to be exemplary only. For example, it will be apparent to those of ordinary skill in the art that the above protocols may be readily modified to use tumor polypeptides to detect antibodies that bind to such polypeptides in a biological sample. The detection of such tumor protein specific antibodies may correlate with the presence of a cancer.

A cancer may also, or alternatively, be detected based on the presence of T cells that specifically react with a tumor protein in a biological sample. Within certain methods, a biological sample comprising $CD4^+$ and/or $CD8^+$ T cells isolated from a patient is incubated with a tumor polypeptide, a polynucleotide encoding such a polypeptide and/or an APC that expresses at least an immunogenic portion of such a polypeptide, and the presence or absence of specific activation of the T cells is detected. Suitable biological samples include, but are not limited to, isolated T cells. For example, T cells may be isolated from a patient by routine techniques (such as by Ficoll/Hypaque density gradient centrifugation of peripheral blood lymphocytes). T cells may be incubated *in vitro* for 2-9 days (typically 4 days) at 37°C with polypeptide (*e.g.*, 5 - 25 μg/ml). It may be desirable to incubate another aliquot of a T cell sample in the absence of tumor polypeptide to serve as a control. For $CD4^+$ T cells, activation is preferably detected by evaluating proliferation of the T cells. For $CD8^+$ T cells, activation is preferably detected by evaluating cytolytic activity. A level of proliferation that is at least two fold greater and/or a level of cytolytic activity that is at least 20% greater than in disease-free patients indicates the presence of a cancer in the patient.

As noted above, a cancer may also, or alternatively, be detected based on the level of mRNA encoding a tumor protein in a biological sample. For example, at least two oligonucleotide primers may be employed in a polymerase chain reaction (PCR) based assay to amplify a portion of a tumor cDNA derived from a biological sample, wherein at least one of the oligonucleotide primers is specific for (*i.e.*, hybridizes to) a polynucleotide encoding the tumor protein. The amplified cDNA is then separated and detected using techniques well known in the art, such as gel electrophoresis. Similarly, oligonucleotide probes that specifically hybridize to a polynucleotide encoding a tumor protein may be used in a hybridization assay to detect the presence of polynucleotide encoding the tumor protein in a biological sample.

To permit hybridization under assay conditions, oligonucleotide primers and probes should comprise an oligonucleotide sequence that has at least about 60%, preferably at least about 75% and more preferably at least about 90%, identity to a portion of a polynucleotide encoding a tumor protein of the invention that is at least 10 nucleotides, and preferably at least 20 nucleotides, in length. Preferably, oligonucleotide primers and/or probes hybridize to a polynucleotide encoding a

polypeptide described herein under moderately stringent conditions, as defined above. Oligonucleotide primers and/or probes which may be usefully employed in the diagnostic methods described herein preferably are at least 10-40 nucleotides in length. In a preferred embodiment, the oligonucleotide primers comprise at least 10 contiguous nucleotides, more preferably at least 15 contiguous nucleotides, of a DNA molecule having a sequence as disclosed herein. Techniques for both PCR based assays and hybridization assays are well known in the art (*see*, for example, Mullis et al., *Cold Spring Harbor Symp. Quant. Biol.*, *51*:263, 1987; Erlich ed., *PCR Technology*, Stockton Press, NY, 1989).

One preferred assay employs RT-PCR, in which PCR is applied in conjunction with reverse transcription. Typically, RNA is extracted from a biological sample, such as biopsy tissue, and is reverse transcribed to produce cDNA molecules. PCR amplification using at least one specific primer generates a cDNA molecule, which may be separated and visualized using, for example, gel electrophoresis. Amplification may be performed on biological samples taken from a test patient and from an individual who is not afflicted with a cancer. The amplification reaction may be performed on several dilutions of cDNA spanning two orders of magnitude. A two-fold or greater increase in expression in several dilutions of the test patient sample as compared to the same dilutions of the non-cancerous sample is typically considered positive.

In another embodiment, the compositions described herein may be used as markers for the progression of cancer. In this embodiment, assays as described above for the diagnosis of a cancer may be performed over time, and the change in the level of reactive polypeptide(s) or polynucleotide(s) evaluated. For example, the assays may be performed every 24-72 hours for a period of 6 months to 1 year, and thereafter performed as needed. In general, a cancer is progressing in those patients in whom the level of polypeptide or polynucleotide detected increases over time. In contrast, the cancer is not progressing when the level of reactive polypeptide or polynucleotide either remains constant or decreases with time.

Certain *in vivo* diagnostic assays may be performed directly on a tumor. One such assay involves contacting tumor cells with a binding agent. The bound binding agent may then be detected directly or indirectly via a reporter group. Such

binding agents may also be used in histological applications. Alternatively, polynucleotide probes may be used within such applications.

As noted above, to improve sensitivity, multiple tumor protein markers may be assayed within a given sample. It will be apparent that binding agents specific for different proteins provided herein may be combined within a single assay. Further, multiple primers or probes may be used concurrently. The selection of tumor protein markers may be based on routine experiments to determine combinations that results in optimal sensitivity. In addition, or alternatively, assays for tumor proteins provided herein may be combined with assays for other known tumor antigens.

The present invention further provides kits for use within any of the above diagnostic methods. Such kits typically comprise two or more components necessary for performing a diagnostic assay. Components may be compounds, reagents, containers and/or equipment. For example, one container within a kit may contain a monoclonal antibody or fragment thereof that specifically binds to a tumor protein. Such antibodies or fragments may be provided attached to a support material, as described above. One or more additional containers may enclose elements, such as reagents or buffers, to be used in the assay. Such kits may also, or alternatively, contain a detection reagent as described above that contains a reporter group suitable for direct or indirect detection of antibody binding.

Alternatively, a kit may be designed to detect the level of mRNA encoding a tumor protein in a biological sample. Such kits generally comprise at least one oligonucleotide probe or primer, as described above, that hybridizes to a polynucleotide encoding a tumor protein. Such an oligonucleotide may be used, for example, within a PCR or hybridization assay. Additional components that may be present within such kits include a second oligonucleotide and/or a diagnostic reagent or container to facilitate the detection of a polynucleotide encoding a tumor protein.

The following Examples are offered by way of illustration and not by way of limitation.

EXAMPLE 1

USE OF MOUSE ANTISERA TO IDENTIFY cDNA SEQUENCES ENCODING LUNG TUMOR ANTIGENS

This example illustrates the isolation of cDNA sequences encoding lung tumor antigens by screening of lung tumor cDNA libraries with mouse anti-tumor sera.

A small cell cDNA lung tumor expression library was constructed using mRNA from the small cell carcinoma cell line NCIH69 employing the Lambda ZAP Express expression system (Stratagene, La Jolla, CA). Mouse anti-SCID mouse serum was developed by growing the lung small cell carcinoma cell lines NCIH69 and NCIH128 in SCID mice, removed SCID serum containing shed and secreted tumor antigens. These sera were pooled and injected into normal mice to produce anti-lung carcinoma serum. The antiserum was adsorbed with *E. coli* lysate and human GAPDH protein, and human PBMC lysate was added to the serum to block antibody to proteins found in normal tissue. The cDNA expression library was then screened with this anti-serum using a goat anti-mouse IgG-A-M (H+L) alkaline phosphatase second antibody developed with NBT/BCIP (Gibco BRL Labs., Gaithersburg, MD). Phage was purified and phagemid excised for clones with inserts in a pBK-CMV vector for expression in prokaryotic or eukaryotic cells.

The determined cDNA sequences for 76 isolated clones are provided in SEQ ID NO:1-76. Comparison of these sequences with those in the public database as described above, revealed no significant homologies to SEQ ID NO:7, 14, 21, 46 and 55. SEQ ID NO:11, 16, 20, 41, 49 and 74 were found to show some homology to previously identified expressed sequence tags (ESTs). The remaining clones were found to show some degree of homology to previously identified genes. The expression levels of certain of the isolated antigens in lung tumor tissues compared to expression levels in 36 normal tissues was determined by microarray technology. The results of these studies are shown below in Table 2, together with the database analyses for these sequences.

Table 2

			Lung Tumor Over-Expression (≥2)			
Clone Name	SEQ ID NO:	Description	LT+F/N	SCC+M/N	Squa/ N	Aden/N
LSC-2	2	CDM, 6C6, BAP31/2	-	-	2.4	-
LSC-6	5	Motor protein p87/89	-	2.2	-	-
LSC-7	6	Ku autoantien 70 kDa	-	2.2	2.3	-
LSC-10	8	PIBF1 protein	-	2.4	-	-
LSC-11	9	Ku autoantien 70 kDa	-	2.4	-	-
LSC-15	11	Novel	-	-	2.9	-
LSC-29	19	Unknown DKFZp586N1020	-	2.5	-	-
LSC-33	22	10 methylene 4 hydrofolate DH	-	2.4	-	-
LSC-39	26	P1 protein	2.4	5.0	2.8	-
LSC-43	27	Minichrom maint deficient	2.3	7.1	2.8	-
LSC-46	28	Non-metastatic cell 1 NME1	2.6	2.5	2.7	2.1
LSC-49	29	GTPase act. Pro. ID-GAP	3.6	10.0	3.8	3.2
LSC-51	30	ZIC family member 2	-	3.4	-	-
LSC-55	32	Transmembrane(63 kDa) ER	2.7	2.2	4.2	2.3
LSC-64	35	Macrophage Migr Inhib Fac	2.6	3.2	3.9	-
LSC-72	38	hRif beta (p102 protein)	2.4	7.0	2.6	-
LSC-76	40	Pro Synth Init. Factor	-	-	-	2.1
LSC-78	42	Motor protein p87/89	-	2.7	2.2	-
LSC-81	43	Epidermal GFR subst 8 EPS8	-	-	2.7	2.1
LSC-101	45	Transmembrane(63 kDa) ER	2.7	-	4.3	-
LSC-103	47	Nuclear factor 4	-	4.3	2.8	-
LSC-134	51	Fumarase	-	3.6	-	-
LSC-142	52	Unknown BAC CTA363M4	-	-	2.5	-
LSC-144	53	Accessory Pro BAP31/BAP2	2.5	-	2.9	2.4
LSC-148	54	Unknown DKFZp586N1020	-	2.2	-	-
LSC-149	55	Novel / Novel	2.6	2.4	3.1	3.5
LSC-163	57	Unknown Ch8p11.2 sect2/19	-	-	-	2.4

LSC-170	58	Unknown PAC DJ0777023	2.2	3.0	2.2	-
LSC-210	74	Novel	-	2.6	2.1	-

LT+F/N = Lung Tumor plus Fetal tissue over Normal tissues
SC+M/N = Lung Small Cell carcinoma plus Metastatic over Normal tissues
Squa/N = Squamous lung tumor over Normal tissues
Aden/N = Adenocarcinoma over Normal tissues

EXAMPLE 2

ISOLATION OF LUNG TUMOR cDNA SEQUENCES BY CONVENTIONAL SUBTRACTION

A human lung squamous cell carcinoma cDNA expression library was constructed from poly A^+ RNA from a pool of two patient tissues using a Superscript Plasmid System for cDNA Synthesis and Plasmid Cloning kit (BRL Life Technologies, Gaithersburg, MD) following the manufacturer's protocol. Specifically, lung carcinoma tissues were homogenized with polytron (Kinematica, Switzerland) and total RNA was extracted using Trizol reagent (BRL Life Technologies) as directed by the manufacturer. The poly A^+ RNA was then purified using an oligo dT cellulose column as described in Sambrook et al., *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratories, Cold Spring Harbor, NY, 1989. First-strand cDNA was synthesized using the NotI/Oligo-dT18 primer. Double-stranded cDNA was synthesized, ligated with BstXI/EcoRI adaptors (Invitrogen, San Diego, CA) and digested with NotI. Following size fractionation with cDNA size fractionation columns (BRL Life Technologies), the cDNA was ligated into the BstXI/NotI site of pcDNA3.1 (Invitrogen) and transformed into ElectroMax *E. coli* DH10B cells (BRL Life Technologies) by electroporation.

Using the same procedure, a normal human lung cDNA expression library was prepared from a pool of normal lung, kidney, colon, pancreas, brain, resting PBMC, heart, skin and esophagus, with esophagus cDNAs making up one third of the material. For both libraries, sequence analysis showed that the majority of clones had a full length cDNA sequence and were synthesized from mRNA

cDNA library subtraction was performed using the above lung squamous cell carcinoma and normal cDNA library, as described by Hara *et al.* (*Blood*, *84*:189-199, 1994) with some modifications. Specifically, a lung squamous cell carcinoma-specific subtracted cDNA library was generated as follows. To from the driver cDNA,

normal tissue cDNA library (80 μg) was digested with BamHI and XhoI, followed by a filling-in reaction with DNA polymerase Klenow fragment. After phenol-chloroform extraction and ethanol precipitation, the DNA was dissolved in 133 μl of H_2O, heat-denatured and mixed with 133 μl (133 μg) of Photoprobe biotin (Vector Laboratories, Burlingame, CA). As recommended by the manufacturer, the resulting mixture was irradiated with a 270 W sunlamp on ice for 20 minutes. Additional Photoprobe biotin (67 μl) was added and the biotinylation reaction was repeated. After extraction with butanol five times, the DNA was ethanol-precipitated and dissolved in 23 μl H_2O to form the driver DNA.

To form the tracer DNA, 10 μg lung squamous cell carcinoma cDNA library was digested with NotI and SpeI, phenol chloroform extracted and passed through Chroma spin-400 columns (Clontech, Palo Alto, CA). Typically, 5 μg of cDNA was recovered after the sizing column. Following ethanol precipitation, the tracer DNA was dissolved in 5 μl H_2O. Tracer DNA was mixed with 15 μl driver DNA and 20 μl of 2 x hybridization buffer (1.5 M NaCl/10 mM EDTA/50 mM HEPES pH 7.5/0.2% sodium dodecyl sulfate), overlaid with mineral oil, and heat-denatured completely. The sample was immediately transferred into a 68 ^{0}C water bath and incubated for 20 hours (long hybridization [LH]). The reaction mixture was then subjected to a streptavidin treatment followed by phenol/chloroform extraction. This process was repeated three more times. Subtracted DNA was precipitated, dissolved in 12 μl H_2O, mixed with 8 μl driver DNA and 20 μl of 2 x hybridization buffer, and subjected to a hybridization at 68 ^{0}C for 2 hours (short hybridization [SH]). After removal of biotinylated double-stranded DNA, subtracted cDNA was ligated into NotI/SpeI site of chloramphenicol resistant pBCSK$^+$ (Stratagene, La Jolla, CA) and transformed into ElectroMax *E. coli* DH10B cells by electroporation to generate a lung squamous cell carcinoma specific subtracted cDNA library (referred to as LST-69).

A cDNA library (referred to as mets3616A) was constructed from a metastatic lung adenocarcinoma. The mets3616A cDNA library was subtracted against a cDNA library prepared from a pool of normal lung, liver, pancreas, skin, kidney, brain and resting PBMC. To increase the specificity of the subtraction, the driver was spiked with genes that were determined to be most abundant in the mets3616A cDNA library, such as EF1-alpha, integrin-beta and anticoagulant protein PP4, as well as with cDNAs

that were previously found to be differentially expressed in subtracted lung adenocarcinoma cDNA libraries. The resulting subtracted library was referred to as mets3616A-S1.

The expression levels of 831 cDNAs from LST-S6 and 521 cDNAs from Mets3616A-S1 in lung tumor tissue and normal tissues was analyzed by microarray technology (Synteni, Palo Alto, CA). Briefly, the cDNAs were PCR amplified and the PCR amplification products were dotted onto slides in an array format, with each product occupying a unique location in the array. mRNA was extracted from the tissue sample to be tested, reverse transcribed, and fluorescent-labeled cDNA probes were generated. The microarrays were probed with the labeled cDNA probes, the slides scanned and fluorescence intensity was measured. This intensity correlates with the hybridization intensity. Thirty-four non-redundant cDNA clones showed 5-fold over-expression in lung tumors, compared with expression in normal tissues tested (lung, skin, lymph node, colon, liver, pancreas, breast, heart, bone marrow, large intestine, kidney, stomach, brain, small intestine, bladder and salivary gland). The determined cDNA sequences for the 34 isolated clones are provided in SEQ ID NO:77-110.

These sequences were compared to known sequences in the gene bank using the EMBL and GenBank databases. The sequences of SEQ ID NO:77, 86, 90 and 108 were found to show some homology to previously identified expressed sequence tags (ESTs). The sequences of SEQ ID NO:78-85, 87-89, 91-107 and 109-110 were found to show some homology to previously identified genes.

The determined cDNA sequences of 54 clones isolated from lung tumor cDNA libraries that were shown to be differentially over-expressed in non-small cell lung carcinoma by are provided in SEQ ID NO:111-142 and 367-395.

EXAMPLE 3

USE OF PATIENT SERA TO IDENTIFY DNA SEQUENCES ENCODING LUNG TUMOR ANTIGENS

This example illustrates the isolation of cDNA sequences encoding lung tumor antigens by expression screening of lung tumor samples with autologous patient sera.

A cDNA expression library was prepared using mRNA from the lung small cell carcinoma cell line NCIH69 in the lambda ZAP Express expression vector (Stratagene) as described above, and screened with a pool of lung small cell carcinoma patient sera. The sera pool was adsorbed with *E. coli* lysate and human PBMC lysate was added to the serum to block antibody to proteins found in normal tissue. Screening was performed as described in Sambrook et al., (*Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratories, Cold Spring Harbor, NY, 1989), with the secondary antibody being goat anti-human IgG-A-M (H + L) conjugated with alkaline phosphatase, developed with NBT/BCIP (Gibco BRL). Positive plaques expressing immunoreactive antigens were purified. Phagemid from the plaques was rescued and the nucleotide sequences of the clones was determined.

The determined cDNA sequences of 86 isolated clones are provided in SEQ ID NO:143-228. The sequences of SEQ ID NO:153, 154, 163, 178, 186, 202, 203, 218 and 219 were found to show some homology to previously identified ESTs. The sequences of SEQ ID NO:143-152, 155-162, 164-177, 179-185, 187-201, 204-217 and 220-228 were found to show some homology to previously isolated genes. The sequences of an additional three isolated clones (referred to as SCC2-16, SCC2-28 and SCC2-620 are provided in SEQ ID NO:437-439.

The expression levels of certain of the isolated antigens in lung tumor tissues compared to expression levels in 36 normal tissues was determined using microarray technology and computer analysis. The results of these studies are shown below in Table 3, together with the database analyses for these sequences.

Table 3

			Lung Tumor Over-Expression (≥2)			
Clone Name	**SEQ ID NO:**	**Description**	**LT+F/N**	**SC+M/N**	**Squa/ N**	**Aden/N**
SCC2-5	146	Unknown KIAA0878	-	3.2	-	2.2
SCC2-9	148	Tubulin K-alpha-1	-	2.2	-	-
SCC2-10	149	NY-REN-64 (pro kinase)	2.0	14.8	3.5	-
SCC2-11	150	TBP-assoc. fact. 2-170	-	5.4	-	-
SCC2-13	152	Centromere Pro F (CENPF)	2.3	5.4	2.8	-
SCC2-14	153	BRUNOL-4	2.7	9.4	3.1	2.3

SCC2-16	437	Non metastatic cells 2	2.3	2.1	2.7	-
SCC2-17	154	Novel (V87915)	2.0	-	2.8	-
SCC2-20	156	Cytoplas Linker Pro 170a2	2.1	3.0+	2.8	-
SCC2-23	157	Hypoxia-induc fact 1 a	2.2	3.0	2.7	-
SCC2-24	158	Actin gamma 1	-	3.8	2.0	-
SCC2-28	438	CHORD-containing pro 1	-	2.1	-	-
SCC2-29	160	Unk. DJ0669I17; ALR-like	2.2	4.0	3.0	2.2
SCC2-31	162	Unknown chrom 1	2.2	3.4	2.8	-
SCC2-36	165	Unknown (T20633)	3.3	2.6	5.5	3.4
SCC2-37	166	Sex-det reg Y Box 21 SOX 2	-	3.0	-	-
SCC2-43	170	CHORD-containing pro 1	-	2.1	-	-
SCC2-50	231	Hypoxia-induc fact 1 a	6.0	3.9	13.7	5.0
SCC2-51	175	Unknown KIAA1051	2.1	3.6	2.0	-
SCC2-54	178	Unknown FLJ20725	-	2.4	2.1	-
SCC2-60	181	Unknown Cosmid R32889	-	3.2	-	-
SCC2-62	439	CHORD-containing pro 1	-	2.1	-	-
SCC2-66	183	Novel, similar to transferase	-	2.2	-	-
SCC2-68	184	Ribosomal pro S7 (RPS7)	-	2.2	-	-

LT+F/N = Lung Tumor plus Fetal tissue over Normal tissues
SC+M/N = Lung Small Cell carcinoma plus Metastatic over Normal tissues
Squa/N = Squamous lung tumor over Normal tissues
Aden/N = Adenocarcinoma over Normal tissues

The expression levels of certain other of the isolated antigens in lung tumor tissues compared to expression levels in 36 normal tissues was determined using microarray technology and either computer or visual analysis. The results of these studies are shown below in Table 4, together with the databank analyses for these sequences. These results indicate that these antigens are over-expressed in lung tumor tissue compared to normal tissue.

Table 4

Clone Name	SEQ ID NO:	Description	Ratio T/N Mean/Med
SCC2-58	180	Sox-2	visual
SCC2-79	190	Mixed-linage leukemia 4 / AF-6	2.0/2.0 sq
SCC2-91	194	Hepatocellular carcinoma-assoc Ag 58	visual
SCC2-100	200	F-Box protein FBW2	visual
SCC2-102	202	Novel	visual
SCC2-104	204	MAP-kinase act death domain MADD	visual
SCC2-143	214	Unknown HSPC232	2.8/2.1 sq
SCC2-266	226	HMG-2	visual

Ratio T/N = lung tumor tissues over normal tissues

EXAMPLE 4

CLONING OF cDNAs ENCODING LUNG SMALL CELL CARCINOMA ANTIGENS

Lung small cell carcinoma antigens were cloned by screening a small cell cDNA expression library with a mouse anti-SCID mouse serum. This antiserum was developed by growing lung small cell carcinoma cell lines NCIH69 and NCIH128 in SCID mice, removing SCID serum containing shed and secreted tumor antigens and immunizing normal mice with this serum. The library was constructed with mRNA from cell line NCIH128 in the lambda ZAP Express expression vector (Stratagene). The antiserum was adsorbed with *E. coli* lysate and human GAPDH protein and Ku autoantigens, and human PBMC lysate was added to the serum to block antibody to proteins found in normal tissue. Table 5 lists the data bank analyses for the nucleotide sequences. The determined cDNA sequences of the clones are provided in SEQ ID NO:258-317.

Table 5

SEQ ID NO:.	Clone ID #	Genbank Homologies
258	54533	Novel
259	54534	Homo sapiens mRNA for LAK-1
260	54536	Homo sapiens CGI-108 protein mRNA
261	54538	Human mRNA for HHR23A protein
262	54540	Homo sapiens chromosome 17, clone hRPC. 1030_0_14
263	55084	Homo sapiens homolog of rat elongation factor p18 (p18)
264	55086	Homo sapiens HSPC194 mRNA
265	54555	Homo sapiens accessory proteins BAP31/BAP29 (DXS1357E) mRNA
266	54557	Homo sapiens mesenchymal stem cell protein DSCD75 mRNA
267	54564	Homo sapiens prp28, U5 snRNP 100 kd protein (U5-100K) mRNA
268	55098	Novel
269	55473	Homo sapiens uroporphyrinogen III synthase (congenital erythropoietic porphyria) (UROS
270	55104	Homo sapiens carbonyl reductase (LOC51181)
271	55105	Homo sapiens membrane component, chromosome 11, surface marker 1 (M11S1)
272	55107	H.sapiens mRNA encoding GPI-anchored protein p137
273	55108	Novel
274	55114	Homo sapiens mRNA; cDNA DKFZp56401716
275	55477	H.sapiens YB-1 gene promoter region
276	55482	Homo sapiens mRNA ; cDNA DKFZp434B0425
277	55483	Human Gu protein mRNA
278	55485	Homo sapiens 45kDa splicing factor mRNA
279	55487	Homo sapiens genomic DNA, chromosome 21q, section 72/105
280	55488	Homo sapiens chromosome 17, clone hCIT529l10
281	55087	Novel (partial overlap of Unknown: Homo sapiens partial mRNA, clone c1-10e16)
282	55089	Homo sapiens scaffold attachment factor A (SAF-A) mRNA
283	55092	Homo sapiens density regulated protein drp1 mRNA
284	55093	H.sapiens mRNA encoding GPI-anchored protein p137
285	56926	Homo sapiens high-mobility group (nonhistone chromosomal) protein 17 (HMG17)
286	56930	Novel
287	56944	Homo sapiens KBNA-2 co-activator (100kD) (p100), mRNA
288	56945	Novel
289	55490	Homo sapiens death-associated protein 6 (DAXX) mRNA, and translated products.

SEQ ID NO:.	Clone ID #	Genbank Homologies
290	55495	Homo sapiens mRNA for MEGF6
291	55504	Mus musculus hairy / enhancer of split 6 mRNA
292	55506	Novel / (136bp: Mus musculus mRNA for Rab24 protein)
293	56480	Novel
294	56482	H.sapiens DNA from chromosome 19-cosmids R31158, R31874, & R28125, genomic seq.
295	56484	Novel
296	56487	Human L23 mRNA for putative ribosomal protein
297	56488	Homo sapiens cDNA FLJ10526 fis, clone NT2RP2000931, highly similar to MATRIN 3
298	56490	Homo sapiens Sul1 isolog mRNA
299	56493	Novel
300	56494	Homo sapiens mRNA; cDNA DKFZp564B167 (from clone DKFZp564B167)
301	56495	Homo sapiens 12p13.3 BAC RPCI11-543P15 (Roswell Park Cancer Inst. Human BAC lib.)
302	56499	Human DNA-binding protein B (dbpB) gene, 3' end
303	56517	Homo sapiens esterase D mRNA
304	56952	Homo sapiens 14q32 Jagged2 gene, complete cds; and unknown gene
305	56953	Homo sapiens DNA polymerase zeta catalytic subunit (REV3L) mRNA
306	56959	Novel
307	57139	Homo sapiens ribosomal protein, large, PO (RPLPO) mRNA
308	57078	Homo sapiens alpha-tubulin isoform 1 mRNA
309	57092	Novel
310	57099	Homo sapiens uncharacterized hypothalamus protein HBEX2 mRNA
311	57100	Novel (last 120 bp: Unknown: Canine 21 kDa Signal peptase subunit mRNA)
312	57105	Homo sapiens splicing factor, arginine/serine-rich 7 (35kD) (SFRS7)
313	57111	Human chromosome 14 DNA sequence
314	57117	Human DNA sequence from cosmid V857G56, between markers DXS366 and DXS87 on chromosome X contains ESTs
315	57121	Homo sapiens genomic DNA of 8p21.3-p22 anti-oncogene of hepatocellular colorectal and non-small cell lung cancer, segment 3/11
316	57124	H.sapiens MLN50 mRNA
317	57125	Homo sapiens calreticulin (CALR) , mRNA

EXAMPLE 5

cDNAs ENCODING LUNG SMALL CELL CARCINOMA ANTIGENS

Lung small cell carcinoma antigens were cloned by screening a small cell cDNA library (NCIH 128) with small cell carcinoma patient sera. The library was contructed with mRNA from cell line NICH 128 in the lambda ZAP Express expression vector (Stratagene). The antiserum was adsorbed with *E. coli* lysate and human GAPDH protein, and human PBMC lysate was added to the serum to block antibody to proteins found in normal tissue. Table 6 lists the homologies identified by database analyses for nucleotide sequences shown in SEQ ID NO:318-364. An additional isolated cDNA sequence (referred to as SCC3-90) is provided in SEQ ID NO:440.

Table 6

SEQ ID NO:	Clone ID #	Genbank Homologies
318	54800	Human Ig germline H-chain G-E-A region B
319	54802	Human mRNA for T-cell cyclophilin
320	54803	Unknown BAC clone GS1-11E15
321	54805	Unknown Homo sapiens cDNA FLJ20272 fis
322	54806	Unknown Homo sapiens mRNA for KIAA0713 protein
323	54809	Unknown Homo sapiens mRNA for RIE2 sid2705
324	54810	Homo sapiens glutamyl-prolyl-tRNA synthetase
325	54813	Unknown Human mRNA for KIAA0262 gene
326	54814	Hu.vacuolar proton pump delta polypeptide (VATD) mRNA
327	54816	Unknown Homo sapiens mRNA for KIAA0713 protein
328	54817	Unknown Hu.Chromosome 16 BAC clone CIT987SK-A-101F10
329	54819	Homo sapiens chromokinesin KIF4 (KIF4) mRNA
330	54821	Unknown Homo sapiens cDNA FLJ11101 fis
331	54823	Human mRNA for heat shock protein hsp86
332	54824	hinge=OXPHOS system complex III mitochondrial subunit
333	54825	H.sapiens mRNA for huntingtin interacting protein HIP-I
334	54826	Homo sapiens kinesin light chain mRNA
335	54827	Homo sapiens kinesin light chain mRNA
336	54829	Novel
337	54830	Unknown complete sequence
338	54832	Unknown Homo sapiens cDNA FLJ20272 fis
339	55800	Homo sapiens mRNA for E-MAP-115/105

SEQ ID NO:	Clone ID #	Genbank Homologies
340	55801	Hu. U-snRNP-associated cyclophilin (USA-CyP) mRNA
341	55803	Human chromosome 14 DNA sequence
342	55804	Human thymosin beta-4 mRNA
343	55805	Homo sapiens huntingtin interacting protein 1 (HIP1)
344	55806	Hu. protein kinase, interferon-inducible double stranded RNA
345	55808	Homo sapiens glutathione S-transferase A4 (GSTA4) mRNA
346	55810	Human chromosome 14 DNA sequence
347	55811	Unknown Homo sapiens mRNA for KIAA0713 protein
348	55812	Novel
349	55814	Human poly(ADP-ribose) synthetase mRNA
350	55816	Novel
351	55817	Homo sapiens centromere protein E (CENPE) mRNA
352	55819	Human poly(ADP-ribose) polymerase mRNA
353	55820	Novel
354	55823	Human mRNA for heat shock protein hsp86
355	55824	Novel
356	55826	Homo sapiens SOX18 mRNA, complete cds
357	55828	Novel
358	55829	Novel
359	55831	Unknown BAC sequence from the SPG4 candidate region
360	55832	Homo sapiens heat shock transcription factor 2 (HSF2
361	55833	Homo sapiens vacuolar H-ATPase subunit D mRNA
362	55834	Homo sapiens clone 628 unknown mRNA
363	55835	Human mRNA for Cu/Zn superoxide dismutase (SOD).
364	55838	Homo sapiens cDNA FLJ20473 fis, clone KAT07092

The expression levels of certain of the isolated antigens in lung tumor tissues compared to expression levels in 36 normal tissues was determined using microarray technology and either computer or visual analysis. The results of these studies are shown below in Table 7, together with the databank analyses for these sequences. These results indicate that these antigens are over-expressed in lung tumor tissue compared to normal tissue.

Table 7

Clone Name	SEQ ID NO:	Description	Ratio T/N Mean/Med
SCC3-5	320	Novel	visual
SCC3-7	321	=SCC3-52; Unknown FLJ20272	visual
SCC3-17	325	Ring finger protein 10	2.1/3.0 ad
SCC3-30	330	Unknown FLJ11101	visual
SCC3-52	338	Unknown cDNA FLJ20272	2.7/1.2 sm
SCC3-64	340	U-snRNP-assoc. cyclophilin	visual
SCC3-71	341	TNG-2	visual
SCC3-79	345	GST A4	visual
SCC3-87	349	Poly(ADP-ribose) synthetase	visual
SCC3-90	440	Polyadenylate binding pro (TIA-1)	visual
SCC3-111	359	Unknown BAC	visual
SCC3-112	360	Heat-shock transcription factor 2	visual

Ratio T/N = lung tumor tissues over normal tissues

EXAMPLE 6

ANALYSIS OF cDNA EXPRESSION USING MICROARRAY TECHNOLOGY

In additional studies, sequences disclosed herein were found to be overexpressed in specific tumor tissues as determined by microarray analysis. Using this approach, cDNA sequences are PCR amplified and their mRNA expression profiles in tumor and normal tissues are examined using cDNA microarray technology essentially as described (Shena *et al.*, 1995). In brief, the clones are arrayed onto glass slides as multiple replicas, with each location corresponding to a unique cDNA clone (as many as 5500 clones can be arrayed on a single slide, or chip). Each chip is hybridized with a pair of cDNA probes that are fluorescence-labeled with Cy3 and Cy5, respectively. Typically, 1μg of polyA$^+$ RNA is used to generate each cDNA probe. After hybridization, the chips are scanned and the fluorescence intensity recorded for both Cy3 and Cy5 channels. There are multiple built-in quality control steps. First, the probe quality is monitored using a panel of ubiquitously expressed genes. Secondly, the control plate also can include yeast DNA fragments of which complementary RNA may be spiked into the probe synthesis for measuring the quality of the probe and the sensitivity of the analysis. Currently, the technology offers a sensitivity of 1 in 100,000

copies of mRNA. Finally, the reproducibility of this technology can be ensured by including duplicated control cDNA elements at different locations.

Clones SCC2-5 (SEQ ID NO:229), SCC2-14 (SEQ ID NO:230), SCC2-50 (SEQ ID NO:231) and SCC2-51 (SEQ ID NO:232) were found to be overexpressed by microarray analysis in adenocarcinoma, lung pleural effusion, squamous cell carcinoma, small cell carcinoma, colon tumor, and ovarian tumor, with low levels of expression being detected in all normal tissues tested. The normal tissues included in the microarray were lymph node, salivary gland, lung, bladder, bone marrow, bronchus, esophagus, kidney, heart, liver, lung, skeletal muscle, spleen, stomach, PBMC, skin, thymus, tonsil, trachea, pituitary gland, adrenal gland, brain, pancreas, thyroid gland, adult lung, colon, small intestine, ovary, and peritoneal epithelium. These cDNAs were cloned from a lung small cell carcinoma expression library using small cell carcinoma patient sera as a probe. SCC2-14 has some similarity to an RNA-binding protein, and SCC2-50 is homologous to hypoxia-inducible factor 1 alpha. Amino acid sequences encoded by these cDNAs (SEQ ID Nos:229-232) are shown in SEQ ID NOs:233-236, respectively.

Also by microarray analysis, SCC2-54 (SEQ ID NO:178) was found to be over-expressed in lung small cell and squamous carcinomas relative to normal tissues. An extended cDNA sequence for this clone is provided in SEQ ID NO:396, encoding the polypeptide sequence set forth in SEQ ID NO:397.

LSC-49 (SEQ ID NO:29) was found to be overexpressed in lung carcinomas, particularly small cell lung carcinomas. An extended sequence for this clone is provided in SEQ ID NO:412, encoding an amino acid sequence set forth in SEQ ID NO:413. Database searches of LSC-49 revealed sequence homology with a GTPase-activating protein for Rac (mgcRacGAP).

The results of an additional microarray analysis, performed using a criteria of greater than or equal to 2-fold over-expression in tumors and the average expression in normal tissues less than or equal to 0.2 (range from 0.01-10), are summarized in Table 8 below.

Table 8

Chip #	Clone ID #	Ratio	Mean Signal 1	Mean Signal 2	SEQ ID NO:
5	56908	3.78	0.837	0.221	398, 243
5	56911	2.29	0.453	0.198	399, 245
5	56912	2.57	0.265	0.103	400, 247
5	56913	2.21	0.306	0.138	401, 249
5	56916	2.44	0.449	0.184	402, 251
5	56917	2.29	0.479	0.209	403, 252
5	56921	2.54	0.418	0.165	404, 253
5	56922	5.05	0.613	0.121	405, 255
5	56923	2.74	0.426	0.155	406, 257

The ratio of signal 1 to signal 2 in Table 8 above provides a measure of the level of expression of the identified sequences in tumor versus normal tissues. For example, for SEQ ID NO:398, the tumor-specific signal was 3.78 times that of the signal for the normal tissues tested; for SEQ ID NO:399, the tumor-specific signal was 2.29 times that of the signal for normal tissues, etc.

Results from an additional microarray analysis, performed using visual analysis for identifying cDNAs over-expressed in selected tumor samples, are provided in Table 9 below. Some of these cDNAs were preferentially over-expressed in small cell lung carcinoma (SCLC) samples even though the original cDNAs were identified from subtracted NSCLC tumor samples.

Table 9

Chip #	Clone ID #	Ratio	Mean Signal 1	Mean Signal 2	SEQ ID NO:
5	60974	3.84	0.584	0.152	407
5	60976	3.73	0.58	0.155	408
5	60977	3.84	0.492	0.128	409
5	60978	4.63	0.476	0.103	410
5	60980	3.4	0.557	0.164	411

In further studies, the expression levels of certain of the isolated antigens in lung tumor tissues previously disclosed in Example 4 were compared to the expression levels in 36 normal tissues using microarray technology and computer analysis. The results of these studies are shown below in Table 10.

Table 10

Clone Name	Clone ID #	SEQ ID NO:	Squa/N	Aden/N	SC/N
LSCC2-1	54533	258	3	2	1
LSCC2-2	54534	259	5	3	5
LSCC2-4	54536	260	3	2	2
LSCC2-8	54540	262	0	3	2
LSCC2-18	55084	263	2	2	1
LSCC2-23	54555	265	2	3	3
LSCC2-25	54557	266	2	1	1
LSCC2-32	54564	267	2	3	2
LSCC2-48	55473	269	4	2	1
LSCC2-58	55104	270	3	5	2
LSCC2-61	55107	272	2	5	3
LSCC2-75	55483	277	2	4	2
LSCC2-79	55487	279	3	2	2
LSCC2-93	55089	282	5	4	4
LSCC2-121	55490	289	4	2	2
LSCC2-127	55495	290	2	4	1
LSCC2-137	55504	291	0	3	8
LSCC2-139	55506	292	3	4	1
LSCC2-161	56480	293	3	2	1
LSCC2-164	56482	294	2	4	2
LSCC2-171	56488	297	6	4	5
LSCC2-178	56494	300	3	5	3
LSCC2-191	56517	303	5	2	2

Squa/N = Squamous lung tumor over Normal tissues
Aden/N = Adenocarcinoma over Normal tissues
SC/N = Lung Small Cell carcinoma over Normal tissues

EXAMPLE 7

FURTHER CHARACTERIZATION OF THE LUNG TUMOR ANTIGEN L43E

The predicted protein sequence shown in SEQ ID NO:436 represents a second open reading frame (ORF-2) encoded by the SCC2-51 cDNA nucleotide sequence (also referred to as L43E). The SCC2-51 nucleotide sequence is shown in SEQ ID NO:175. This protein sequence has 33% identity and 49% similarity to the pol polyprotein of the fish Takifgu rubripes retrotransposon. Motif searches indicate potential protease signatures and protein translocation analysis indicates that the protein

could be cytoplasmic or membrane-associated due to a potential transmembrane region. Using realtime PCR, SCC2-51 was found to be over-expressed in primary small cell carcinoma and in atypical carcinoid metastatic tumors, but weakly expressed in other lung carcinomas and normal tissues except for pituitary gland and adrenal gland. The cDNA sequence and ORF-1 have homology to Takifugu rubrupes gag polyprotein (28% identity and 45% similarity).

EXAMPLE 8

ISOLATION OF CDNA SEQUENCES FOR ADDITIONAL LUNG TUMOR ANTIGENS

Additional cDNA clones were obtained from analysis II of LST-S6 and Mets3616-S1 libraries of Lung Chip V. These cDNAs were differentially expressed in lung squamous and/or adenocarcinoma tumors (greater than or equal to 2 fold), and the average expression values for these clones in normal tisues were below 0.1 (the range of value was between 0.001 and 10). A total of 29 non-redundant cDNA sequences were isolated and are disclosed in SEQ ID NO:367-395. A summary of these clones with respect to the Genbank searches is shown in Table 11.

Table 11

SEQ ID NO:	Clone ID #	Chip #	GenBank
367	49949	5	Novel
368	49952	5	Collagen type IV alpha-5
370	49960	5	h. mRNA for Pirin, isolate 17
371	49961	5	vector/Novel
372 and 373	49962	5	HBP, heme binding protein
374	49965	5	h. testitin
375	49966	5	KIAA 1077
376	49977	5	Cyclin B homologue
377	49975	5	Cat Eye 22q11.2
378	49982	5	Novel
379	49986	5	Novel
380	49988	5	KIAA0292, similar to AR1 protein
381	49993	5	transferrin receptor
382	49995	5	Cathepsin B
383	49996	5	RP3, similar to mouse tctex-1
384	49999	5	Novel, Cosmid g1572c198
385	50006	5	sheep and mouse sox2 gene (HMG box, germ cell)
386	50007	5	Nrf3 for NF-E2 related factor 3
387	50009	5	vector/Novel, chrom. 10 seq
388	50014	5	clone RP5-1025A1 on 20p11.21
389	50016	5	Failed/h. MEGF9
390	50017	5	NH0160k17
391	50019	5	None
392	50022	5	h mitotic kinesin-like protein-1
393	50023	5	KIAA1077
394	50024	5	None
395	50033	5	None

EXAMPLE 9

REAL-TIME PCR ANALYSIS OF L578S

As previously shown in Example 2, clone 48137 (SEQ ID NO:89), which is also referred to as L578S, and is predicted to have an extended cDNA sequence of SEQ ID NO:365, was shown to be 5-fold over-expressed in lung tumors as compared to the normal tissue by microarray analysis. Real-time PCR analysis confirmed that L578S is over-expressed in both lung squamous and adenocarcinoma tumors. Database analysis identified two human proteins showing some degree of homology to L578S, one corresponding to a putative type Ib membrane-bound protein. Protein alignment between this protein and SEQ ID NO:365 indicated that L578S full-length protein may also be a type Ib membrane-protein. This indicates that L578S is an attractive target for the development of antibody-based therapeutics.

EXAMPLE 10

SYNTHESIS OF POLYPEPTIDES

Polypeptides are synthesized on a Perkin Elmer/Applied Biosystems Division 430A peptide synthesizer using FMOC chemistry with HPTU (O-Benzotriazole-N,N,N',N'-tetramethyluronium hexafluorophosphate) activation. A Gly-Cys-Gly sequence is attached to the amino terminus of the peptide to provide a method of conjugation, binding to an immobilized surface, or labeling of the peptide. Cleavage of the peptides from the solid support is carried out using the following cleavage mixture: trifluoroacetic acid:ethanedithiol:thioanisole:water:phenol (40:1:2:2:3). After cleaving for 2 hours, the peptides are precipitated in cold methyl-t-butyl-ether. The peptide pellets are then dissolved in water containing 0.1% trifluoroacetic acid (TFA) and lyophilized prior to purification by C18 reverse phase HPLC. A gradient of 0%-60% acetonitrile (containing 0.1% TFA) in water (containing 0.1% TFA) is used to elute the peptides. Following lyophilization of the pure fractions, the peptides are

characterized using electrospray or other types of mass spectrometry and by amino acid analysis.

From the foregoing it will be appreciated that, although specific embodiments of the invention have been described herein for purposes of illustration, various modifications may be made without deviating from the spirit and scope of the invention. Accordingly, the invention is not limited except as by the appended claims.

CLAIMS

1. An isolated polynucleotide comprising a sequence selected from the group consisting of:

(a) sequences provided in SEQ ID NO:1-232, 243-396, 398-412, 414-424 and 437-440;

(b) complements of the sequences provided in SEQ ID NO:1-232, 243-396, 398-412, 414-424 and 437-440;

(c) sequences consisting of at least 20 contiguous residues of a sequence provided in SEQ ID NO:1-232, 243-396, 398-412, 414-424 and 437-440;

(d) sequences that hybridize to a sequence provided in SEQ ID NO:1-232, 243-396, 398-412, 414-424 and 437-440, under moderately stringent conditions;

(e) sequences having at least 75% identity to a sequence of SEQ ID NO:1-232, 243-396, 398-412, 414-424 and 437-440;

(f) sequences having at least 90% identity to a sequence of SEQ ID NO:1-232, 243-396, 398-412, 414-424 and 437-440; and

(g) degenerate variants of a sequence provided in SEQ ID NO:1-232, 243-396, 398-412, 414-424 and 437-440.

2. An isolated polypeptide comprising an amino acid sequence selected from the group consisting of:

(a) SEQ ID NO:229-232, 237-242, 397, 413 and 425-436;

(b) sequences encoded by a polynucleotide of claim 1; and

(c) sequences having at least 70% identity to a sequence encoded by a polynucleotide of claim 1; and

(d) sequences having at least 90% identity to a sequence encoded by a polynucleotide of claim 1.

3. An expression vector comprising a polynucleotide of claim 1 operably linked to an expression control sequence.

4. A host cell transformed or transfected with an expression vector according to claim 3.

5. An isolated antibody, or antigen-binding fragment thereof, that specifically binds to a polypeptide of claim 2.

6. A method for detecting the presence of a cancer in a patient, comprising the steps of:

(a) obtaining a biological sample from the patient;

(b) contacting the biological sample with a binding agent that binds to a polypeptide of claim 2;

(c) detecting in the sample an amount of polypeptide that binds to the binding agent; and

(d) comparing the amount of polypeptide to a predetermined cut-off value and therefrom determining the presence of a cancer in the patient.

7. A fusion protein comprising at least one polypeptide according to claim 2.

8. An oligonucleotide that hybridizes to a sequence recited in SEQ ID NO:1-232, 243-396, 398-412, 414-424 and 437-440 under moderately stringent conditions.

9. A method for stimulating and/or expanding T cells specific for a tumor protein, comprising contacting T cells with at least one component selected from the group consisting of:

(a) polypeptides according to claim 2;

(b) polynucleotides according to claim 1; and

(c) antigen-presenting cells that express a polypeptide according to claim 1,

under conditions and for a time sufficient to permit the stimulation and/or expansion of T cells.

10. An isolated T cell population, comprising T cells prepared according to the method of claim 9.

11.. A composition comprising a first component selected from the group consisting of physiologically acceptable carriers and immunostimulants, and a second component selected from the group consisting of:

(a) polypeptides according to claim 2;

(b) polynucleotides according to claim 1;

(c) antibodies according to claim 5;

(d) fusion proteins according to claim 7;

(e) T cell populations according to claim 10; and

(f) antigen presenting cells that express a polypeptide according to claim 2.

12. A method for stimulating an immune response in a patient, comprising administering to the patient a composition of claim 11.

13. A method for determining the presence of a cancer in a patient, comprising the steps of:

(a) obtaining a biological sample from the patient;

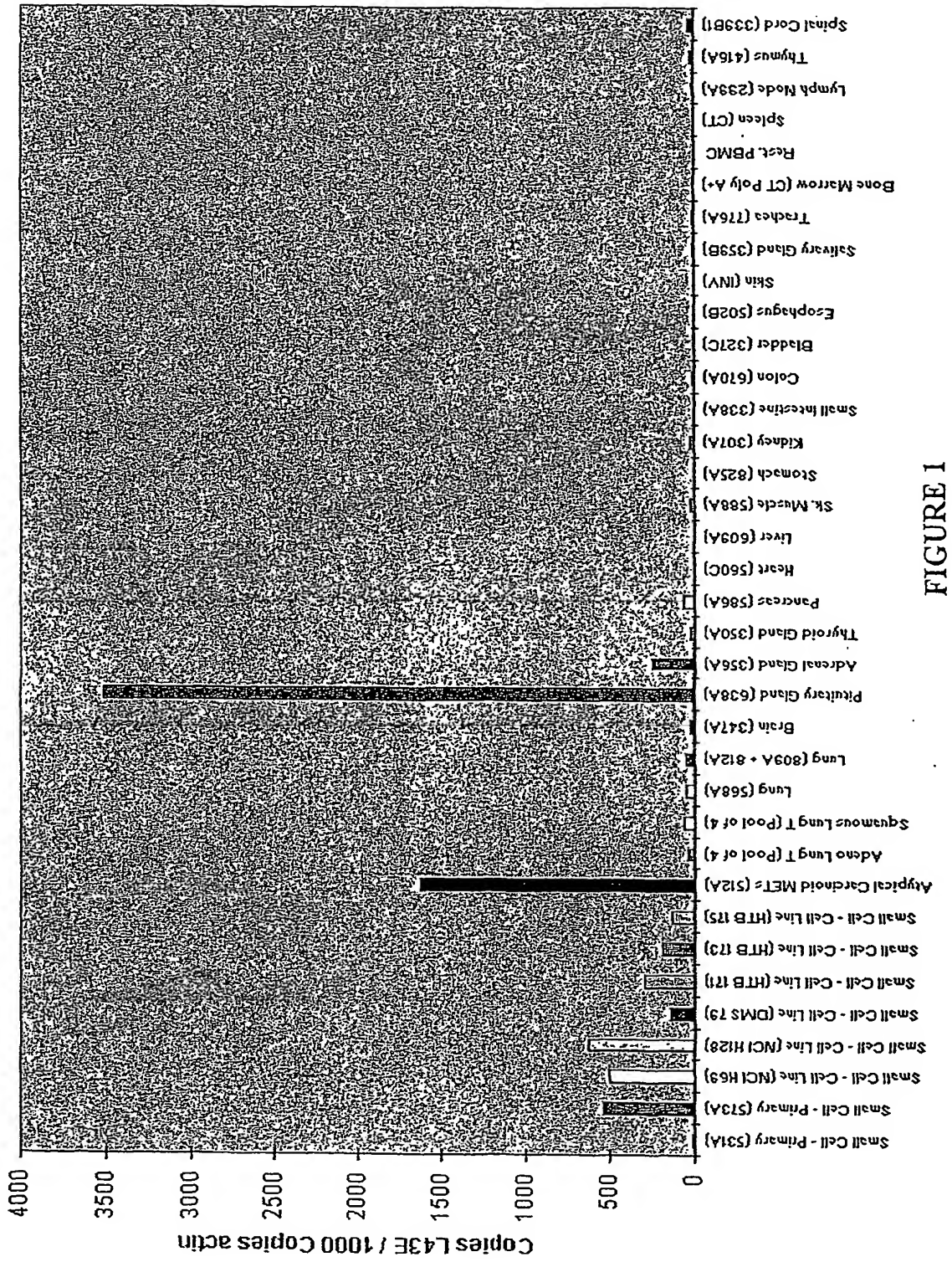
(b) contacting the biological sample with an oligonucleotide according to claim 8;

(c) detecting in the sample an amount of a polynucleotide that hybridizes to the oligonucleotide; and

(d) compare the amount of polynucleotide that hybridizes to the oligonucleotide to a predetermined cut-off value, and therefrom determining the presence of the cancer in the patient.

14. A diagnostic kit comprising at least one oligonucleotide according to claim 8.

15. A diagnostic kit comprising at least one antibody according to claim 5 and a detection reagent, wherein the detection reagent comprises a reporter group.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Atypical Carcinoid MET= (512A)
Adeno Lung T (Pool of 4)
Squamous Lung T (Pool of 4)
Lung (568A)
Lung (803A + 812A)
Brain (347A)
Pituitary Gland (638A)
Adrenal Gland (356A)
Thyroid Gland (350A)
Pancreas (586A)
Heart (560C)
Liver (603A)
Sk. Muscle (588A)
Stomach (825A)
Kidney (307A)
Small Intestine (338A)
Colon (610A)
Bladder (327C)
Esophagus (502B)
Skin (INV)
Salivary Gland (353B)
Trachea (776A)
Bone Marrow (CT Poly A+)
Resr. PBMC
Spleen (CT)
Lymph Node (233A)
Thymus (416A)
Spinal Cord (333B1)

FIGURE 1

SEQUENCE LISTING

<110> Corixa Corporation
Lodes, Michael J.
Wang, Tongtong
Mohamath, Raodoh
Indirias, Carol Y.

<120> COMPOSITIONS AND METHODS FOR THE THERAPY AND DIAGNOSIS OF LUNG CANCER

<130> 210121.512PC

<140> PCT
<141> 2001-04-11

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actataaata ttcaggaaga gatagtttga ttttttggt tgatgcctcc aaggctatgt 180
ttgaatctca gagtgaagat gagttgacac cttttgacat gagcatccag tgtatccaaa 240
gtgtgtacat cagtaagatc ataagcagtg atcgagatct cttggctgtg gtgttctatg 300
gtacccgaga aagacaaaaa ttcagtgaat tttaaaaata tttacgtctt acaggagctg 360
gataatccag gtgcaaaacg aattctagac tttgccagtt taaggggcag caggg 415

<210> 19
<211> 466
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(466)
<223> n = A,T,C or G

<400> 19
gaattcggca cnagcgggga tcggtcgcct gagaggtatc acctcttctg ggctcaagat 60
ggacaacaag aagcgcctgg cctacgccat catccagttc ctgcatgacc agctccggca 120
cgggggcctc tcgtccgatg ctcaggagag cttggaagtc gccatccagt gcctggagac 180
tgcgtttggg gtgacggtag aagacagtga ccttgcgctc cctcagactc tgccggagat 240
atttgaagcg gctgccacgg gcaaggagat gccgcaggac ctgaggagcc ccgcgcgaac 300
cccgcctttc cgaagaagga ctcancaaga agggcaagaa gccgccttca aaacccgaaa 360
gggaaaaccg aagccagaat gaaaaagtgg gaaaaacttt tgaaagcttg cccgtgccat 420
ttttcttacc gggaaaaaag cccattcgga agcttcaaac ccccaa 466

<210> 20
<211> 296
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(296)
<223> n = A,T,C or G

<400> 20
gaattcggca cnaggtggtg tgtggctgcg gcctgggcaa gagccgccgc ggaccatgag 60
ctgagtaagt tctggaggga tcctgcctct tggagccttc gcagccaggc agctgtgaac 120

tgtgagctag agtgaagcag aaatctagga agatgagctc caagatggtc ataagtgaac 180
caggactgaa ttgggatatt tcccccaaaa atggccttaa gacatttttc tctcagaaaa 240
ttataaagat cattccatgg cttccaagtt taaaaagaac ttacgtggtt tttatc 296

<210> 21
<211> 328
<212> DNA
<213> Homo sapien

<400> 21
gaattcggca cgagcccgcg ctgcacttgc tcgccgcgtg actggaggac cgagccccca 60
cattttcttt atgtggttgt ggtgggggca cagtaatgcc ctgtgcgccg tagcgttcct 120
gtggggatgt ggccgggggg cgtcgggaag cgtcactgct tgatgtccga gctcagcgat 180
gaagccagcg agccggaact cctgaaccgc agcttgtcca tgtggcacgg gctcgggaca 240
caggtcagcg gggaggagct ggatgtcccc ctggatcttc acacagctgc ttcattggcc 300
agtatgaagt ggtgaaggaa tgtgtgca 328

<210> 22
<211> 466
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(466)
<223> n = A,T,C or G

<400> 22
gaattcggca cgaggcggac taataaaggc catggcgcca gcagaaatcc tgaacgggaa 60
ggagatctcc gcgcaaataa gggcgagact gaaaaatcaa gtcactcagt tgaaggagca 120
agtacctggt ttcacaccac gcctggcaat attacaggtt ggcaacagag atgattccaa 180
tctttatata aatgtgaagc tgaaggctgc tgaagagatt gggatcaaag ccactcacat 240
taagttacca agaacaacca cagaatctga ggtgatgaag tacattacat ctttgaatga 300
agactctact gtacatgggt tcttagtgca gctaccttta gattcagaga attccattaa 360
cactgaagaa gtgatcaatg ctattgcacc cganaaggat gtggatggat tgactagcat 420
caatgctggg aaacttgcta gaggtgacct caatgactgt ttcatt 466

<210> 23
<211> 517
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(517)
<223> n = A,T,C or G

<400> 23
gaattcggca cgagcagagg tctccagagc cttctctctc ctgtgcaaaa tggcaactct 60
taaggaaaaa ctcattgcac cagttgcgga agaagaggca acagttccaa acaataagat 120
cactgtagtg ggtgttggac aagttggtat ggcgtgtgct atcagcattc tgggaaagtc 180
tctggctgat gaacttgctc ttgtggatgt tttggaagat aagcttaaag gagaaatgat 240
ggatctgcag catgggagct tatttcttca gacacctaaa attgtggcag ataaagatta 300
ttctgtgacc gccaattcta agattgtagt ggtaactgca ggagtccgtc agcaagaagg 360
ggagagtcgg ctcaatctgg tgcagagaaa tgttaatgtc ttcaaattca ttattcctca 420
gatcgtcaag tacagtcctg attgcatcat aattgtggnt tccaacccag tggacattct 480
tacgtatgtt acctggaaac taagtggatt acccaaa 517

<210> 24

<211> 196
<212> DNA
<213> Homo sapien

<400> 24
gaattcggca cgagggtggc actatgtggc gcgtctgtgc gcgacgggct cagaatgtag 60
ccccatgggc gggactcgag gctcggtgga cggccttgca ggaggtaccc ggaactccac 120
gagtgacctc gcgatctggc ccggctcccg ctcgtcgcaa cagcgtgact acagggtatg 180
gcggggtccg ggcact 196

<210> 25
<211> 365
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(365)
<223> n = A,T,C or G

<400> 25
gaattcggca cgaggttggg cggtgctggt ttttcgctcg tcgactgcgg ctcttcctcg 60
ggcagcggaa gcggcgcggc ggtcggagaa gtggcctaaa acttcggcgt tgggtgaaag 120
aaaatggccc gaaccaagca gactgctcgt aagtccaccg gtgggaaagc cccccgcaaa 180
cagctggcca cgaaagccgc caggaaaagc gctccctcta ccggcggggt gaagaagcct 240
catcgctaca ggcccgggac cgtggcgctt cganagattc gtcgttatca gaagtcgacc 300
gagctgctca tccggaagct gcccttccag angttggtga gggagatcgc gcaggatttc 360
aaaac 365

<210> 26
<211> 321
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(321)
<223> n = A,T,C or G

<400> 26
ctcgagtttt ttttttttt tttttttgta cgaaatggct aagtttattc aacatctcgg 60
atattcatct ggatattggg tttgttttgt gatacaatac atattcacct taactggtgc 120
tactgcaaag aaagctttct tgacctgcat gacgtgcctc anagcttctc tccaccaatt 180
ggaaccaccc aaagcctagt ctanaccaaa gtgctctgga gaaaaaaaac aaaacaaaaa 240
aacagcaaac agaaaacagt tgtgccccca aaagtactca gaagtcatat gttatttaca 300
attgggtttg tgtgggatgg g 321

<210> 27
<211> 454
<212> DNA
<213> Homo sapien

<400> 27
gaattcggca cgagcaagga tgaggagaac aatccccttg agacagaata tggcctttct 60
gtctacaagg atcaccagac catcaccatc caggagatgc cggagaaggc cccagccggc 120
cagctccccc gctctgtgga cgtcattctg gatgatgact tggtggataa agcgaagcct 180
ggtgaccggg ttcaggtggt gggaacctac cgttgccttc ctggaaagaa gggaggctac 240
acctctggga ccttcaggac tgtcctgatt gcctgtaatg ttaagcagat gagcaaagga 300
tgctcagccc tctttctctg ctgaggatat agccaagatc aagaagttca gtaaaacccg 360

atccaaggat atctttgacc atctggccaa gtcattggcc ccaagtatcc atgggcatga 420
ctatgtcaag aaagcaatcc tctgcttgct cttg 454

<210> 28
<211> 285
<212> DNA
<213> Homo sapien

<400> 28
gaattcggca cgaggttggt ctgaaattca tgcaagcttc cgaagatctt ctcaaggaac 60
actacgttga cctgaaggac cgtccattct ttgccggcct ggtgaaatac atgcactcag 120
ggccggtagt tgccatggtc tgggaggggc tgaatgtggt gaaaacgggc cgagtcatgc 180
tcggggagac caaccctgca gactccaagc ctgggaccat ccgtggagac ttctgcatac 240
aagttggcag gaacattata catggcagtg attctgtgga gagtg 285

<210> 29
<211> 512
<212> DNA
<213> Homo sapien

<400> 29
gaattcggca cgagcaacct tgtaaatgtg aaagtacaac tcgtatttat ctctgatgtg 60
ccgctggctg aactttgggt tcatttgggg tcaaagccag tttttctttt aaaattgaat 120
tcattctgat gcttggcccc catacccccа accttgtcca gtggagccca acttctaaag 180
gtcaatatat catcctttgg catcccaact aacaataaag agtaggctat aagggaagat 240
tgtcaatatt ttgtggtaag aaaagctaca gtcatttttt ctttgcactt tggatgctga 300
aatttttccc atggaacata gccacatcta gatagatgtg agcttttttct tctgttaaaa 360
ttattcttaa tgtctgtaaa aacgattttc ttctgtagaa tgtttgactt cgtattgacc 420
cttatctgta aaacacctat ttgggataat atttggaaaa aaagtaaata gctttttcaa 480
aatgaaaaaa aaaaaaaaaa aaaaaactcg ag 512

<210> 30
<211> 464
<212> DNA
<213> Homo sapien

<400> 30
gaattcggca cgaggccagg tgggcagccc gcggaccgac ccctactcgg cggcgcaact 60
ccacaaccag tacggcccca tgaatatgaa catgggtatg aacatggcag cagccgcggc 120
ccaccaccac caccaccacc accaccaccc cggtgccttt ttcccgctat atgcggcagc 180
agtgcatcaa gcaggagcta atctgcaagt ggatcgaccc cgagcaactg agcaatccca 240
agaagagctg caacaaaact ttcagcacca tgcacgagct ggtgacacac gtctcggtgg 300
agcacgtcgg cggcccggag cagagcaacc acgtctgctt ctgggaggag tgtccgcgcg 360
agggcaagcc cttcaaggcc aaatacaaac tggtcaacca catccgcgtg cacacaggcg 420
agaaaccctt cccctgcccc ttcccgggct gtggcaaagt cttc 464

<210> 31
<211> 317
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(317)
<223> n = A,T,C or G

<400> 31
gaattcggca cgagcagagg tgagcaagct ggaacagcaa tgccagaagc agcaggagca 60
ggctgacagc ctggaacgca gcctcgaggc tgagcgggcc tcccgggctg agcgggacag 120

tgctctggag actctgcagg gccagttaga ggagaaggcc cangagctag ggcacagtca 180
gagtgcctta gcctcggccc aacgggagtt ggctgccttc cgcaccaagg tacaagacca 240
cagcaaggct gaagatgagt ggaaggccca gttggcccgg ggccggcaag aggctganag 300
gaaaaatagc ctcatca 317

<210> 32
<211> 275
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(275)
<223> n = A,T,C or G

<400> 32
gaattcggca cgagcgaagg aggacggagg cttcagacac tcggaagcct ttgaggcact 60
ccagcaaaag agtcagggac tggactccag gctccagcac gtggaggatg gggtgctctc 120
catgcaggtg gcttctgcgc gccagaccga gagcctggag tccctcctgt ncaagagcca 180
ggagcacgag cagcgcctgg ccgccctgca ggggcgcctg gaaggcctcg ggtcctcata 240
ggcanaccan gatggcctgc cagcacggtg aggag 275

<210> 33
<211> 516
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(516)
<223> n = A,T,C or G

<400> 33
gaattcggca cgaggggccc tgggcgttga ctgtgggaaa ctcggaaaca agctcacatc 60
ttcctgtggg aaaccttcta gcaacaggat gagtctgcag tggactgcag ttgccacctt 120
cctctatgcg gaggtctttg ttgtgttgct tctctgcatt tccttcattt ctcctaaaag 180
atggcagaag attttcaagt cccggctggt ggagttgtta gtgtcctatg gcaacacctt 240
ctttgtggtt ctcattgtca tccttgtgct gttggtcatc gatgccgtgc gcgaaattcg 300
gaagtatgat gatgtgacgg aaaaggtgaa cctccagaac aatcccgggg ccatggagca 360
cttccacatg aagnttttcc gtgcccagag gaatctctac attgctggct tttccttgct 420
gctgtccttc ctgcttagac gcctggtgac tctcatttcc aacaggccac gctgctggcc 480
ttcaatgaac ctttaaaaac aggcggagag tnctat 516

<210> 34
<211> 446
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(446)
<223> n = A,T,C or G

<400> 34
gaattcggca cgagacagaa atgnctaaag aagagaagga ccctggaatg ggtgcaatgg 60
gtggaatggg aggtggtatg ggaggtggca tgttctaact cctagactag tgctttacct 120
ttattaatga actgtgacag gaagcccaag gcagtgttcc tcccaataac ttcagagaag 180
tcanttggag aaaatgaaga aaaaggctgg ctgaaaatca ctataaccat cagttactgg 240
tttcagttga caaaatatat aatggtttac tgctgtcatt gtccatgcct acagataatt 300

tattttgtat ttttgaataa aaaacatttg tacattcctg atactgggta caagagccat 360
gtaccagtgt actgctttca acttaaatca ctgaggcatt tttactacta ttctgttaaa 420
atcaggattt tagtgcttgc ccccca 446

<210> 35
<211> 440
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(440)
<223> n = A,T,C or G

<400> 35
gaattcggca cgaggtttat ttgtccccac cagaaggttg gggtgggcgg gcctagaaca 60
cagcgtgcgg cgggttcccg ggtggagcca gcgcagacag cgtgggtccc tgcggctctt 120
angcgaaggt ggagttgttc cancccacat tggcccgcgt ttcattgtcg taatagttga 180
tgtagaccct gtccgggctg atgcgcaggc gctctgccag caggccgcac agcagcttgc 240
tgtaggagcg gttctgcgcg ccgccgatct tgccgatgct gtgcangctg canagcgcgc 300
acggctcgct ggagccgccg aaggccatga gctggtccgg gaccacgtgc accgctatgt 360
actgggggg cttgccggtg gcctgcgcca nctgctgggt gagctcggag aggaaccgtc 420
cggcacggag gcgcggggca 440

<210> 36
<211> 373
<212> DNA
<213> Homo sapien

<400> 36
gaattcggca cgaggccaaa cgtaccaaga aagtcgggat cgtcggtaaa tacgggaccc 60
gctatggggc ctccctccgg aaaatggtga agaaaattga aatcagccag cacgccaagt 120
acacttgctc tttctgtggc aaaaccaaga tgaagagacg agctgtgggg atctggcact 180
gtggttcctg catgaagaca gtggctggcg gtgcctggac gtacaatacc acttccgctg 240
tcacggtaaa gtccgccatc agaagactga aggagttgaa agaccagtag acgctcctct 300
actctttgag acatcactgg cctataataa atgggttaat ttatgtaaca aaaaaaaaaa 360
aaaaaaactc gag 373

<210> 37
<211> 565
<212> DNA
<213> Homo sapien

<400> 37
gaattcggca cgaggggca cgggcacccc cgcggtcccc gggaggctag agatcatgga 60
agggaagtgg ttgctgtgta tgttactggt gcttggaact gctattgttg aggctcatga 120
tggacatgat gatgatgtga ttgatattga ggatgacctt gacgatgtca ttgaagaggt 180
agaagactca aaaccagata ccactgctcc tccttcatct cccaaggtta cttacaaagc 240
tccagttcca acaggggaag tatattttgc tgattctttt gacagaggaa ctctgtcagg 300
gtggatttta tccaaagcca agaaagacga taccgatgat gaaattgcca aatatgatgg 360
aaagtgggag gtagaggaaa tgaaggagtc aaagcttcca ggtgataaag gacttgtgtt 420
gatgtctcgg gccaagcatc atgccatctc tgctaaactg aacaagccct tcctgtttga 480
caccaagcct ctcttgttca gtatgaggtt aatttccaaa atggaataga atgtggtggt 540
gcctatgtga aactgctttc taaaa 565

<210> 38
<211> 566
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(566)
<223> n = A,T,C or G

<400> 38
gaattcggca cgagcccaac tttagccagg aagatcagca ggacacccag atttatgaga 60
agcatgacaa ccttctacat gggaccaaga agaaaaagga gaagatggtg agtgcagcat 120
tcatgaagaa gtacatccat gtggccaaaa tcatcaagcc tgtcctgaca caggagtcgg 180
ccacctacat tgcagaagag tattcacgcc tgcgcagcca ggatagcatg agctcagaca 240
ccgccaggac atctccagtt acagcccgaa cactggaaac tctgattcga ctggccacag 300
cccatgcgaa ggcccgcatg agcaagactg tggacctgca ggatgcagag gaagctgtgg 360
agttggtcca gtatgcttac tttaagaagg ttctggagaa ggagaagaaa cgtaagaagc 420
gaagtgagga tgaatcagag acagaagatg aagaggagaa aagccaagag gaccaggagc 480
agaagaggaa gagaaggaag actcgccagc cagatgccaa agatggggat tcatacgacc 540
cctatgactt cagtgacaca gaggan 566

<210> 39
<211> 364
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(364)
<223> n = A,T,C or G

<400> 39
gaattcggca cgaggtctca cagaaagttc tccgctccca gacatgggtc cctcggcttc 60
ctgcctcgga agcgcagcag caggcatcgt gggaaggtga agagcttccc taaggatgac 120
ccgtccaagc cggtccacct cacagccttc ctgggataca aggctggcat gactcacatc 180
gtgcgggaag tcgacaggcc gggatccaag gtgaacaaga aggaggtggt ggaggctgtg 240
accattgtag agacaccacc catggtggtt gtgggcattg tgggctacgt ggaaacccct 300
ngaggcctcc ggacctttaa gactgtcttt gcttgagcac atcantgatg aatgcaagag 360
gcgt 364

<210> 40
<211> 336
<212> DNA
<213> Homo sapien

<400> 40
gaattcggca cgagcccaga tctcctaccc agcctcccag ggggcctact acatccctgg 60
acaggggcgt tccacatacg ttgtcccgac acagcagtac cctgtgcagc caggagcccc 120
aggcttctat ccaggtgcaa gccctacaga atttgggacc tacgctggcg cctactatcc 180
agcccaaggg gtgcagcagt ttcccactgg cgtggccccc gccccagttt tgatgaacca 240
gccaccccag attgctccca agagggagcg taagacgatc cgaattcgag atccaaacca 300
aggaggaaag gatatcacag aggagatcat gtctgg 336

<210> 41
<211> 566
<212> DNA
<213> Homo sapien

<400> 41
gaattcggca cgagacttgg gaaaatgaat tcagaggagg aagatgaagt gtggcaggtg 60
atcataggag ccagagctga gatgacttca aaacaccaag agtacttgaa gctggaaacc 120
acttggatga ctgcagttgg tctttcagag atggcagcag aagctgcata tcaaactggc 180

gcagatcagg cctctataac cgccaggaat cacattcagc tggtgaaact gcaggtggaa 240
gaggtgcacc agctctcccg gaaagcagaa accaagctgg cagaagcaca gatagaagag 300
ctccgtcaga aaacacagga ggaaggggag gagcgggctg agtcggagca ggaggcctac 360
ctgcgtgagg attgagggcc tgagcacact gccctgtctc cccactcagt ggggaaagca 420
ggggcagatg ccaccctgcc cagggttggc atgactgtct gtgcaccgag aagaggcggc 480
aggtcctgcc ctgccaatca ggcgagacgc ctttgtgagc tgtgagtgcc tcctgtggtc 540
tcaggcttgc gcttggacct ggttct 566

<210> 42
<211> 386
<212> DNA
<213> Homo sapien

<400> 42
gaattcggca cgagggcagc tcgagtccac cagcagcgcc gtccgcttga ccgagatgct 60
gcgggcctgt cagttatcgg gtgtgaccgc cgccgcccag agttgtctct gtgggaagtt 120
tgtcctccgt ccattgcgac catgccgcag atactctact tcaggcagct ctgggttgac 180
tactggcaaa attgctggag ctggcctttt gtttgttggt ggaggtattg gtggcactat 240
cctatatgcc aaatgggatt cccatttccg ggaaagtgta gagaaaacca taccttactc 300
agacaaactc ttcgagatgg ttcttggtcc tgcagcttat aatgttccat tgccaaagaa 360
atcgattcaa gtcgggtcca ctaaaa 386

<210> 43
<211> 514
<212> DNA
<213> Homo sapien

<400> 43
gaattcggca cgagggcaaa acctccacct cctgatgaat ttcttgactg tttccaaaag 60
tttaaacacg gatttaacct tctggccaaa ctgaagtctc atattcagaa tcctagtgct 120
gcagatttgg ttcacttttt gtttactcca ttaaatatgg tggtgcaggc aacaggaggt 180
cctgaactag ccagttcagt acttagtccc ctattgaata aggacacaat tgatttctta 240
aattatactg tcaatggtga tgaacggcag ctgtggatgt cattgggagg aacttggatg 300
aaagccagag cagagtggcc aaaagaacag tttattccac catatgttcc acgattccgc 360
aatggctggg agcccccaat gctgaacttt atgggagcca caatggaaca agatctttat 420
caactggcag aatctgtggc aaatgtagca gaacatcagc gcaaacagga aataaaaaga 480
ttatcccaga gcatttcagt gtatcagaat atta 514

<210> 44
<211> 467
<212> DNA
<213> Homo sapien

<400> 44
gaattcggca cgagactaga gccgcatcac atggggactt ctgcaaatac agagactcgg 60
attaaaggtg gagaagatgg agctaaagga actgcttatt taatacattt gaacaacttt 120
tggggtactt agaaggtgct ttgaaacctg catttgatta agcaagaatt cgcttgcaag 180
ttaaggggca ctccacagaa ggatgttatt atcaagtcag atgcaccgga cactttgtta 240
ttggagaaac atgcagatta tatcgcatcc tatggctcaa agaaagatga ttatgaatac 300
tgtatgtctg agtatttgag aatgagtggc atctattggg gtctgacagt aatggatctc 360
atgggacaac ttcatcgcat gaatagagaa gagattctgg catttattaa gtcttgccaa 420
catgaatgtg gtggaataag tgctagtatc ggacatgatc ctcatct 467

<210> 45
<211> 344
<212> DNA
<213> Homo sapien

<220>

<221> misc_feature
<222> (1)...(344)
<223> n = A,T,C or G

<400> 45
gaattcggca cgagggagac tggaggaaga gctccgccag ctgaagtccg attcccacgg 60
gccgaaggag gacggaggct tcagacactc ggaagccttt gaggcactcc agcaaaagag 120
tcagggactg gactccaggc tccagcacgt ggaggatggg gtgctctcca tgcaagtggc 180
ttctgcgcgc cagaccgaga gcctggagtc cctcctgtcc aagaaccagg aacacgagca 240
gcgcctggcc gcctgcaggg gcgcctggaa agcctcgggt cctcagaagc agaccangat 300
ggcctgccag cacngtgagg agcctgggcg agacccagct ggtg 344

<210> 46
<211> 303
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(303)
<223> n = A,T,C or G

<400> 46
gaattcggca cgagngggaa cacaagtatg tgccaccaca ccttggtaac ttttaaattg 60
tttttagata tgaggtctga ccatgttgcc catgccatta ttattccttt tgataaaggt 120
gaatttaggc taaactgtga aagaatgtac agcaaatggc tctgttaatt cttctcatag 180
gaggacaggt tactgttaat agagaacata tgtatgtaat ggctaaaaat agggcagtag 240
aaaaggaatg taacttctca cctccttga gaatgnaaag aaagaaagaa aaaaggatgg 300
tac 303

<210> 47
<211> 364
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(364)
<223> n = A,T,C or G

<400> 47
gaattcggca cgaganatag ttcctttctc taaagtggat gaggaacaaa tgaaatataa 60
atcggagggg aagtgcttct ctgttttggg attttgtaaa tcttctcagg ttcagagaag 120
attcttcatg ggaaatcaag ttctaaaggt ctttgcagca agagatgatg aggcagctgc 180
agttgcactt tcctccctga ttcatgcttt ggatgactta gacatggtgg ccatagttcg 240
atatgcttat gacaaaagag ctaatcctca agtcggcgtg gcttttcctc atatcaagca 300
taactatgag tgtttagtgt atgtgcagct gcctttcatg gaagacttgc ggcaatacat 360
gttt 364

<210> 48
<211> 284
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(284)
<223> n = A,T,C or G

<400> 48
gaattcggca cgagagcagc tggaggcact ggagaaggag aaggctgcca agctggagat 60
tctgcagcag caacttcagg tggctaatga agcccgggac agtgcccaga cctcagtgac 120
acaggcccag cgggagaagg cagagctgag ccggaaggtg gaggaactcc aggcctgtgt 180
tgagacagcc cgccaggaac agcatgaggc ccaggcccag gttgcagagc tagagttgca 240
gctgcggtct gagcagcaaa aagcaactga ganagaaagg gtgg 284

<210> 49
<211> 313
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(313)
<223> n = A,T,C or G

<400> 49
gaattcggca cgaggtttat tatagctcat acctgggacc gattaaggtg tcaacatttt 60
aaaattactc aagatattaa ccagaaaaga tgattatggc ctttaaaact attggacaaa 120
ctgatgctat ttaacattgt tcacagccat ttaatttgaa taacaaattt tagattctaa 180
gtaggccata acttctttgc aaaacaattg atttataaag gtacagtttc agaaggnaac 240
agcatgagac tagtcttcct ataggcacat tttagtagac tgctcttctc atccctggtc 300
aaggagcttc tct 313

<210> 50
<211> 522
<212> DNA
<213> Homo sapien

<400> 50
gaattcggca cgagggacag ccaacaaaag cagcttcttg aagttcaact tcagcaaaat 60
aaggagctgg aaaataaata tgctaaatta gaagaaaagc tgaaggaatc tgaggaagca 120
aatgaggatc tgcggaggtc ctttaatgcc ctacaagaag agaaacaaga tttatctaaa 180
gagattgaga gtttgaaagt atctatatcc cagctaacaa gacaagtaac agccttgcaa 240
gaagaaggta ctttaggact ctatcatgcc cagttaaaag taaaagaaga agaggtacac 300
aggttaagtg ctttgttttc ctcctctcaa aagagaattg cagaactgga agaagaattg 360
gtttgtgttc aaaaggaagc tgccaagaag gtaggtgaaa ttgaagataa actgaagaaa 420
gaattaaagc atcttcatca tgatgcaggg ataatgagaa atgaaactga aacagcagaa 480
gagagagtgg cagagctagc aagagatttg gtggagatgg aa 522

<210> 51
<211> 463
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(463)
<223> n = A,T,C or G

<400> 51
gaattcggca cgaggagcac ttcggctcct cgcgcgctcg cgtcccctcg tgcgggctcc 60
agccgcagcc ttagcttcgg ctcccggctt gggtggcgcg gccgtgccct cgttttggcc 120
tccgaacgcg gctcgaatgg caagccaaaa ttccttccgg atagaatatg ataccttttgg 180
tgaactaaag gtgccaaatg ataagtatta tggcgcccag accgtgagat ctacgatgaa 240
ctttaagatt ggaggtgtga cagaacgcat gccaacccca gttattaaag cttttggcat 300
cttgaagcga gcggccgctg aagtaaacca ggattatggt cttgatccaa agattgctan 360
tgcaataatg aaggcagcag angaggtagc tgaaggtaaa ttaaatgatc attttcctct 420

cgtggtatgg cagactggat caggaactca gacaaatatg aat 463

<210> 52
<211> 423
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(423)
<223> n = A,T,C or G

<400> 52
gaattcggca cgagaaagcg cagccgagcc cagcgccccg cacttttctg agcagacgtc 60
cagagcagag tcagccagca tgaccgagcg ccgcgtcccc ttctcgctcc tgcggggccc 120
cagctgggac cccttccgcg actggtaccc gcatagccgc ctcttcgacc aggccttcgg 180
gctgccccgg ctgccggagg agtggtcgca gtggttaggc ggcagcagct ggccaggcta 240
cgtgcgcccc ctgcccccg ccgccatcga gagccccgca gtggccgcgc ccgcctacag 300
ccgcgcgctc agccggcaac tcagcagcgg ggtctcggag atccggcaca ctgcggaccg 360
ctggcgcgtg tccctggatg tcaaccactt cgccccggac gagctgacgg tcaagaccaa 420
nga 423

<210> 53
<211> 474
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(474)
<223> n = A,T,C or G

<400> 53
gaattcggca cgagggaatc tctacattgc tggcttttcc ttgctgctgt ccttcctgct 60
tagacgcctg gtgactctca tttcgcagca ggccacgctg ctggcctcca atgaagcctt 120
taaaaagcag gcggagagtg ctagtgaggc ggccaagang tacatggagg agaatgacca 180
gctcaagaan ggagctgctg ttgacggagg caagttggat gtcgggaatg ctgaggtgaa 240
gttggaggaa gagaacagga gcctgaaggc tgacctgcag aagctaaagg acgagctggc 300
cagcactaag caaaaactag agaaagctga aaaccaggtt ctggccatgc ggaagcagtc 360
tgagggcctc accaaggagt acgaccgctt gctggaggag cacgcaaagc tgcaggctgc 420
agtagatggt cccatggaca agaaggaaga gtaagggcct tccttcctcc cctg 474

<210> 54
<211> 473
<212> DNA
<213> Homo sapien

<400> 54
gaattcggca cgagctcgtg ccgaatcggc acgagggatc ggtcgcctga gaggtatcac 60
ctcttctggg ctcaagatgg acaacaagaa gcgcctggcc tacgccatca tccagttcct 120
gcatgaccag ctccggcacg ggggcctctc gtccgatgct caggagagct tggaagtcgc 180
catccagtgc ctggagactg cgtttggggt gacggtagaa gacagtgacc ttgcgctccc 240
tcagactctg ccggagatat ttgaagcggc tgccacgggc aaggagatgc cgcaggacct 300
gaggagccca gcgcgaaccc cgccttccga ggaggactca gcagaggcag agcgcctcaa 360
aaccgaagga aacgagcaga tgaaagtgga aaactttgaa gctgccgtgc atttctacgg 420
aaaagccatc gagctcaacc cagccaacgc cgtctatttc tgcaacagaa gcc 473

<210> 55
<211> 365

<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(365)
<223> n = A,T,C or G

<400> 55
gaattcggca cgagtgattg aggatcagtt gggtgccaga cactctctta ggtgtcagag 60
ctccagttta cattacacag ataaggtccc tgccccccag cgaagctggc attaaagtca 120
gcaaataaat gttcaggatt ttgataagtg ctgtaaagga aaaaagacct gtaacagggt 180
ggaatgactg gggagggggc gaggctctat ctaggcaggg atggaccaga cntgagagtg 240
accaggaggt tcgagccagt tgcagaggga caagaaaggc cttctgggca ggggcactta 300
caggtacaga gcccctgcag cagaataagc ttctcctacc ggagaggcaa aaagaaggcc 360
ttttg 365

<210> 56
<211> 517
<212> DNA
<213> Homo sapien

<400> 56
gaattcggca cgagggacgc cgctttgttg cctgagatga agttggagcc cttgtttttg 60
acattggatc ctatactgtg agagctggtt atgctggtga ggactgcccc aaggtggatt 120
ttcctacagc tattggtatg gtggtagaaa gagatgacgg aagcacatta atggaaatag 180
atggcgataa aggcaaacaa ggcggtccca cctactacat agatactaat gctctgcgtg 240
ttccgaggga gaatatggag gccatttcac ctctaaaaaa tgggatggtt gaagactggg 300
atagtttcca agctattttg gatcatacct acaaaatgca tgtcaaatca gaagccagtc 360
tccatcctgt tctcatgtca gaggcaccgt ggaatactag agcaaagaga gagaaactga 420
cagagttaat gtttgaacac tacaacatcc ctgccttctt cctttgcaaa actgcagttt 480
tgacagcatt tgctaatggt ccgttctact gggcttg 517

<210> 57
<211> 237
<212> DNA
<213> Homo sapien

<400> 57
gaattcggca cgagctatga gatagtatta agcaattaaa agaatatatg acttttctac 60
atcaaaattt gaaacttctg tgcatcaaag gacacaatca acagagtgaa gaggaaactt 120
acagaatggg agaaaatatt tgtaaatcat gtatctcata aggattaata tccaggctat 180
gtaaagaact acatctcaac acaaaaacac aaacagcttg attaaaaaat gggcaaa 237

<210> 58
<211> 485
<212> DNA
<213> Homo sapien

<400> 58
gaattcggca cgagcgcggc ggtcactgcg ccggggtagt gggccccagt gttgcgctct 60
ctggccgttc cttacacttt gcttcaggct ccagtgcagg ggcgtagtgg gatatggcca 120
actcgggctg caaggacgtc acgggtccag atgaggagag ttttctgtac tttgcctacg 180
gcagcaacct gctgacagag aggatccacc tccgaaaccc ctcggcggcg ttcttctgtg 240
tggcccgcct gcaggatttt aagcttgact ttggcaattc ccaaggcaaa acaagtcaaa 300
cttggcatgg agggatagcc accatttttc agagtcctgg cgatgaagtg tggggagtag 360
tatggaaaat gaacaaaagc aatttaaatt ctctggatga gcaagaaggg gttaaaagtg 420
gaaatgtatg ttgtaataga agttaaaagt tgccaacttc aagaaaggaa aaaaaaaata 480
acctg 485

<210> 59
<211> 514
<212> DNA
<213> Homo sapien

<400> 59
gaattcggca cgagtggcgt tggaggtcgg cgatatggaa gatgggcagc tttccgactc 60
ggattccgac atgacggtcg cacccagcga caggccgctg caattgccaa aagtgctagg 120
tggcgacagt gctatgaggg ccttccagaa cacggcaact gcatgtgcac cagtatcaca 180
ttatcgagct gttgaaagtg tggattcaag tgaagaaagt ttttctgatt cagatgatga 240
tagctgtctt tggaaacgca aacgacagaa atgttttaac cctcctccca aaccagagcc 300
ttttcagttt ggccagagca gtcagaaacc acctgttgct ggaggaaaga agattaacaa 360
catatggggt gctgtgctgc aggaacagaa tcaagatgca gtggccactg aacttggtat 420
cttgggaatg gagggcacta ttgacagaag cagacaatcc gagacctaca attatttgct 480
tgccaagaaa cttaggaagg aatctcaaga gcat 514

<210> 60
<211> 336
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(336)
<223> n = A,T,C or G

<400> 60
gaattcggca cgaggccgcc gggtgctggt caccggggca ggcaaaggta tagggcgcgg 60
cacggtccag gcgctgcacg cgacgggcgc gcgggtggtg gctgtgagcc ggactcaggc 120
ggatcttgac agccttgtcc gcgagtgccc ggggatagaa cccgtgtgcg tggacctggg 180
tgactgggag gccaccgagc gggcgctggg cagcgtgggc cccgtggacc tgctggtgaa 240
caacgccgct gtcgccctgc tgcagccctt nctggaggtc accaaggagg cctttgacag 300
atcctttgag gtgaacctgc gtgcggtcat ccaggt 336

<210> 61
<211> 515
<212> DNA
<213> Homo sapien

<400> 61
gaattcggca cgaggtcgcc tgagaggtat cacctcttct gggctcaaga tggacaacaa 60
gaagcgcctg gcctacgcca tcatccagtt cctgcatgac cagctccggc acgggggcct 120
ctcgtccgat gctcaggaga gcttggaagt cgccatccag tgcctggaga ctgcgtttgg 180
ggtgacggta gaagacagtg accttgcgct ccctcagact ctgccggaga tatttgaagc 240
ggctgccacg ggcaaggaga tgccgcagga cctgaggagc ccagcgcgaa ccccgccttc 300
cgaggaggac tcagcagagg cagagcgcct caaaaccgaa ggaaacgagc agatgaaagt 360
ggaaaacttt gaagctgccg tgcatttcta cggaaaagcc atcgagctca acccagccaa 420
cgccgtctat ttctgcaaca gagccgcagc ctacagcaaa ctcggcaact acgcaggcgc 480
ggtgcaggac tgtgagcggg ccatctgcat tgacc 515

<210> 62
<211> 417
<212> DNA
<213> Homo sapien

<400> 62
gaattcggca cgagagccaa cctcctggaa gggcacgcgc gtgctgaggt gtaccttca 60
gccaagccaa tgatcaaatt ccaatcaccc tatgaggaac agttggaaca gcagagactg 120

gcagtgcagc aggtggagga ggcccagcag ctgcgggaac accaggaagc tttgcaccag 180
cagaggctgc aggggcactt actacggcag caggaacagc agcagcagca ggtggcaaga 240
gagatggccc tgcagaggca ggctgagctt gaggagggcc ggccgcagca ccaggagcag 300
ctccggcagc aagctcatta tgatgctatg gataatgata tcgttcaggg agcagaggac 360
cagggaatcc aaggagagga aggagcctat gaaagagaca accagcacca agatgaa 417

<210> 63
<211> 455
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(455)
<223> n = A,T,C or G

<400> 63
gaattcggca cgagggccgg gcttgggctg cgtggagaat acttttgcg atgcctactg 60
gagactttga ttcgaagccc agttgggccg accaggtgga ggaggagggg gaggacgaca 120
aatgtgtcac cagcgagctc ctcaagggga tccctctggc cacaggtgac accagcccag 180
agccaganct actgccggga gctccactgc cgcctcccaa ggaggtcatc aacggaaaca 240
taaagacagt gacagagtac aagatagatg aggatggcaa gaagttcaag attgtccgca 300
ccttcaggat tgagacccgg aaggcttcaa aggctgtcgc aaggaggaag aactggaaga 360
agttcgggaa ctcagagttt gacccccccg gacccaatgt ggccaccacc actgtcagtg 420
acgatgtctc tatgacgttc atcaccagca aagag 455

<210> 64
<211> 517
<212> DNA
<213> Homo sapien

<400> 64
gaattcggca cgagccatgt tggggtttgt gggtcgggtg gccgctgctc cggcctccgg 60
ggccttgcgg agactcaccc cttcagcgtc gctgccccca gctcagctct tactgcgggc 120
cgctccgacg gcggtccatc ctgtcaggga ctatgcggcg caaacatctc cttcgccaaa 180
agcaggcgcc gccaccgggc gcatcgtggc ggtcattggc gcagtggtgg acgtccagtt 240
tgatgaggga ctaccaccaa ttctaaatgc cctggaagtg caaggcaggg agaccagact 300
ggttttggag gtggcccagc atttgggtga gagcacagta aggactattg ctatggatgg 360
tacagaaggc ttggttagag gccagaaagt actggattct ggtgcaccaa tcaaaattcc 420
tgttggtcct gagactttgg gcagaatcat gaatgtcatt ggagaaccta ttgatgaaag 480
aggtcccatc aaaaccaaac aatttgctcc cattcat 517

<210> 65
<211> 519
<212> DNA
<213> Homo sapien

<400> 65
gaattcggca cgagtggagg tcggcgatat ggaagatggg cagctttccg actcggattc 60
cgacatgacg gtcgcaccca gcgacaggcc gctgcaattg ccaaaagtgc taggtggcga 120
cagtgctatg agggccttcc agaacacggc aactgcatgt gcaccagtat cacattatcg 180
agctgttgaa agtgtggatt caagtgaaga aagtttttct gattcagatg atgatagctg 240
tctttggaaa cgcaaacgac agaaatgttt taaccctcct cccaaaccag agccttttca 300
gtttggccag agcagtcaga aaccacctgt tgctggagga aagaagatta acaacatatg 360
gggtgctgtg ctgcaggaac agaatcaaga tgcagtggcc actgaacttg gtatcttggg 420
aatggagggc actattgaca gaagcagaca atccgagacc tacaattatt tgcttgccaa 480
gaaacttagg aaggaatctc aagagcattc caaaagatc 519

<210> 66

<211> 517
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(517)
<223> n = A,T,C or G

<400> 66
gaattcggca cgagggcggc tgaggaaagc aggaggaggt ggcggcggcg ggaagatggc 60
tccttcacct accaaacgca aagaccgctc agatgagaag tccaaggatc gctcaaaaga 120
taaaggggcc accaaggagt cgagtgagaa ggatcgcggc cgggacaaaa cccgaaagag 180
gcgcagcgct tccagtggta gcagcagtac caggtctcgg tccagctcga cttccagctc 240
aggctccagc accagcactg gctcaagcag tggctccagc tcttcctcag catccagccg 300
ctcaggaagc tccagcacct cccgcagctc cagctctagc agctcttctg gctctccaag 360
tccttctcgg cgcanacacg acaacaggag gcgctcccgc tccaaatcca aaccacctaa 420
aagagatgaa aaggagagga aaaggcggag cccatctcct aagcccacca aagtgcacat 480
tgggagactc acccggaatg tgacaaagga tcacatc 517

<210> 67
<211> 517
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(517)
<223> n = A,T,C or G

<400> 67
gaattcggca cgaggcgccg tgcagcggct gagtgtnngc ggcggcgacg gcaaacccgg 60
agctgccggc cggcgcgcgg gaggaggacg cgggtgcggt ctaggaaacg gagctgcggg 120
cggaggctcc atgttgggaa gcggcgccgt tcgtgcttgt tagcgggaat ccgggagccg 180
cggggtgagc tggcgggggc cgggccctaa gtgaagatgg aggccccgct gcggcctgcc 240
gcggacatcc tgaggcggaa cccgcagcag gactacgaac tcgtccagag ggtcggcagc 300
ggcacctacg gggacgtcta taaggccaga aatgtacaca caggagagct ggctgcagta 360
aaaatcatta aattggagcc tggagatgat ttttctttga ttcaacaaga aatatttatg 420
gttaaagaat gtaaacattg taacatcgtt gcctactttg ggagttatct tagtcgggaa 480
aaactatgga tttgtatgga atactgtggt ggcggat 517

<210> 68
<211> 516
<212> DNA
<213> Homo sapien

<400> 68
gaattcggca cgaggtcggt tcctgctatt ccggtttctc cactccgtcc cccgcgggtc 60
tgctctgtgt gccatggacg gcattgtccc agatatagcc gttggtacaa agcggggatc 120
tgacgagctt ttctctactt gtgtcactaa cggaccgttt atcatgagca gcaactcggc 180
ttctgcagca aacggaaatg acagcaagaa gttcaaaggt gacagccgaa gtgcaggcgt 240
cccctctaga gtgatccaca tccggaagct ccccatcgac gtcacggagg gggaagtcat 300
ctccctgggg ctgccctttg ggaaggtcac caacctcctg atgctgaagg ggaaaaacca 360
ggccttcatc gagatgaaca cggaggaggc tgccaacacc atggtgaact actacacctc 420
ggtgacccct gtgctgcgcg gccagcccat ctacatccag ttctccaacc acaaggagct 480
gaagaccgac agctctccca accaggcgcg ggccca 516

<210> 69
<211> 455

<212> DNA
<213> Homo sapien

<400> 69
gaattcggca cgaggagcca tagagcctct gcctcgatgc cgttttgccc ccgctctttg 60
gacacgccga cccggcgctc cccaaggaat gctgtcccaa caagattccc gtgaaagagc 120
acccgtgtcg ccccctcccg tggacttctg tgccgccccg tccacacctg ttcttgggtg 180
catgtgggtt ttcggttcct ggcggtccag gacggggcgg gggctcccct cccatctcgt 240
gctgggaggt ctcagcgcgc tctcctgtcc ctgggacgtg cgtctctcct tctcatgccg 300
ttctggaaaa tgctcttgct gtagagagca gctgcttctg ccagggtgtt ggaggtggtg 360
gagcgccttc cgattccatt catggcattt tgtgatgtga tgtaattgga atagagctgt 420
tgatttaagg caaaaaaaaa aaaaaaaaac tcgag 455

<210> 70
<211> 569
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(569)
<223> n = A,T,C or G

<400> 70
gaattcggca cgagcagaac gcagctctgc tctgctngag gaggtgcaga gcctccggga 60
ggaggctgag aaacagcggg tggcttcaga gaacctgcgg caggagctga cctcacaggc 120
tgagcgtgcg gaggagctgg gccaagaatt gaaggcgtgg caggagaagt tcttccagaa 180
agagcaggcc ctctccaccc tgcagctcga gcacaccagc acacaggccc tggtgagtga 240
gctgctgcca gctaagcacc tctgccagca gctgcaggcc gagcaggccg ctgccgagaa 300
acgccaccgt gaggagctgg agcagagcaa gcaggccgct gggggactgc gggcagagct 360
gctgcgggcc cagcgggagc ttggggagct gattcctctg cggcagaagg tggcagagca 420
ggagcgaaca gctcagcagc tgcgggcaga gaaggccagc tatgcagagc agctgagcat 480
gctgaagaag gcgcatggcc tgctggcaga ggagaaccgg gggctgggtg agcgggccaa 540
ccttggccgg cagtttctgg aagtggagt 569

<210> 71
<211> 555
<212> DNA
<213> Homo sapien

<400> 71
gaattcggca cgagtggcga cgccccctaa gcggcgggcg gtggaggcca cgggggagaa 60
agtgctgcgc tacgagacct tcatcagtga cgtgctgcag cgggacttgc gaaaggtgct 120
ggaccatcga gacaaggtat atgagcagct ggccaaatac cttcaactga gaaatgtcat 180
tgagcgactc caggaagcta agcactcgga gttatatatg caggtggatt tgggctgtaa 240
cttcttcgtt gacacagtgg tcccagatac ttcacgcatc tatgtggccc tgggatatgg 300
ttttttcctg gagttgacac tggcagaagc tctcaagttc attgatcgta agagctctct 360
cctcacagag ctcagcaaca gcctcaccaa ggactccatg aatatcaaag cccatatcca 420
catgttgcta gaggggctta gagaactaca aggcctgcag aatttcccag agaagcctca 480
ccattgactt cttcccccca tcctcagaca ttaaagagcc tgaatgccaa aaaaaaaaaa 540
aaaaaaaaac tcgag 555

<210> 72
<211> 567
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature

<222> (1)...(567)
<223> n = A,T,C or G

<400> 72
gaattcggca cgagggctgg tggagttgtt agtgtnctat ggcaacacct tctttgtggt 60
tctcattgtc atccttgtgc tgttggtcat cgatgccgtg cgcgaaattc ggaagtatga 120
tgatgtgacg gaaaaggtga acctccagaa caatcccggg gccatggagc acttccacat 180
gaagcttttc cgtgcccaga ggaatctcta cattgctggc ttttccttgc tgctgtcctt 240
cctgcttaga cgcctggtga ctctcatttc gcagcaggcc acgctgctgg cctccaatga 300
agcctttaaa aagcaggcgg agagtgctag tgaggcggcc aagaagtaca tggaggagaa 360
tgaccagctc aagaagggag ctgctgttga cggaggcaag ttggatgtcg ggaatgctga 420
ggtgaagttg gaggaagaga acaggagcct gaaggctgac ctgcagaagc taaaggacga 480
gctggccagc actaagcaaa aactagagaa agctgaaaac caggttctgg ccatgcggaa 540
gcagtctgag ggcctcacca aggagta 567

<210> 73
<211> 254
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(254)
<223> n = A,T,C or G

<400> 73
gaattcggca cgagcctgga caaggagaga gtgcggntgc tgagagccga gcccagcaat 60
cccgatcctc tgagtcgtga agaagggagg cagcgagggg gttggggttg gggcctgagg 120
caagccccca ggctccgctc ttgccagagg gacaggagcc atggctcaga aaatggactg 180
tggtgcgggc ctcctcggct tccaggctga ggcctccgta gaagacagcg ccttgcttat 240
gcagaccttg atgg 254

<210> 74
<211> 516
<212> DNA
<213> Homo sapien

<400> 74
gaattcggca cgagcagccc tcggctgagc cgcgccgcac catgcccgcc gtggacaagc 60
tcctgctaga ggaggcgttg caggacagcc cccagactcg ctctttactg agcgtgtttg 120
aagaagatgc tggcaccctc acagactata ccaaccagct gctccaggca atgcagcgcg 180
tctatggagc ccagaatgag atgtgcctgg ccacacaaca gctttctaag caactgctgg 240
catatgaaaa acagaacttt gctcttggca aaggtgatga agaagtaatt tcaacactcc 300
actatttttc caaagtggtg gatgagctta atcttctcca tacagagctg gctaaacagt 360
tggcagacac aatggttcta cctatcatac aattccgaga aaaggatctc acagaagtaa 420
gcactttaaa ggatctattt ggactcgcta gcaatgagca tgacctctca atggcaaaat 480
acagcaggct gcctaagaaa aaggagaatg agaagg 516

<210> 75
<211> 468
<212> DNA
<213> Homo sapien

<400> 75
gaattcggca cgagcaggga cgacgcccag aatgggagct gactgatatg gtggtgtggg 60
tgactggagc ctcgagtgga attggtgagg agctggctta ccagttgtct aaactaggag 120
tttctcttgt gctgtcagcc agaagagtgc atgagctgga aagggtgaaa agaagatgcc 180
tagagaatgg caatttaaaa gaaaaagata tacttgtttt gccccttgac ctgaccgaca 240
ctggttccca tgaagcggct accaaagctg ttctccagga gtttggtaga atcgacattc 300

tggtcaacaa tggtggaatg tcccagcgtt ctctgtgcat ggataccagc ttggatgtct 360
acagaaagct aatagagctt aactacttag ggacggtgtc cttgacaaaa tgtgttctgc 420
ctcacatgat cgagaggaag caaggaaaga ttgttacttg tgaatagc 468

<210> 76
<211> 349
<212> DNA
<213> Homo sapien

<400> 76
gaattcggca cgagctcgac tcttagcttg tcggggacgg taaccgggac ccggtgtctg 60
ctcctgtcgc cttcgcctcc taatccctag ccactatgcg tgagtgcatc tccatccacg 120
ttggccaggc tggtgtccag attggcaatg cctgctggga gctctactgc ctggaacacg 180
gcatccagcc cgatggccag atgccaagtg acaagaccat tgggggagga gatgactcct 240
tcaacacctt cttcagtgag acgggcgctg gcaagcacgt gccccgggct gtgtttgtag 300
acttggaacc cacagtcatt gatgaagttc gcactggcac ctaccgcca 349

<210> 77
<211> 469
<212> DNA
<213> Homo sapien

<400> 77
ataggcacat acacatacac agtctcagca aggttataaa gaaccctgtc aggtccactt 60
gcaacatggc cttgctactt ggattagctc ctttaagcct gaaaataact ttcctggtca 120
tggaagaact ggacgcatct tttaacttat gaaatagaag ttgaacttga aaactctttt 180
taaaaaatcc tggttttgca ggacagctac ataatgaatg tatatattaa gactgtagct 240
gaattgcaca tgaaatcaga ttgccaactt cttgactttc aatgttagac atttatcctt 300
aagttgtgag cgatatatgt agcatgctgt gaaatgtctg ttatagctct ttaattcatc 360
agtattaata cagaattatc atttgcgttt cttggtactt tttattcaat gtaatcagaa 420
gctgtgatgt tttgcctttg tagtcctgtg ctttggtact gtaattttt 469

<210> 78
<211> 399
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(399)
<223> n = A,T,C or G

<400> 78
gcgctcggtt tgagggctcg gcgcggggtt tcctgttcct tcttctgcgc ggctgcagct 60
cgggacttcg gcctgaccca gcccccatgg cttcagaaga gctacagaaa gatctagaag 120
aggtaaaggt gttgctggaa aaggctacta ggaaaagagt acgtgatgcc cttacagctg 180
aaaaatccaa gattgagaca gaaatcaaga acaagatgca acagaaatca cagaagaaag 240
canaacttct tgataatgaa aaaccagctg ctgtggttgc tcccattaca acgggctata 300
cggtgaaaat cagtaattat ggatgggatc aagtcagata agtttgtgaa aatctacatt 360
accttaactg gagttcatca agttcccact gagaatgtg 399

<210> 79
<211> 439
<212> DNA
<213> Homo sapien

<400> 79
ccgagaagct gggctttgct ggtcttgtac aggagatctc atttgggaca actaaggata 60
aaatgctggt catcgagcag tgtaagaact ccagagctgt aaccatttt attagaggag 120

gaaataagat gatcattgag gaggcgaaac gatcccttca cgatgctttg tgtgtcatcc 180
ggaacctcat ccgcgataat cgtgtggtgt atggaggagg ggctgctgag atatcctgtg 240
ccctggcagt tagccaagag gcggataagt gccccacctt agaacagtat gccatgagag 300
cgtttgccga cgcactggag gtcatcccca tggccctctc tgaaaacagt ggcatgaatc 360
ccatccagac tatgaccgaa gtccgagcca gacaggtgaa ggagatgaac cctgctcttg 420
gcatcgactg tttgcacaa 439

<210> 80
<211> 437
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(437)
<223> n = A,T,C or G

<400> 80
aattaacatc ttttttgttt aggcatgttc aattaatgct gtagctatca tagctntgct 60
cttacctgaa gccttgtccc caccacacag gacagccttc ctcctgaaga gaatgtcttt 120
gtgtgtccga agttgagatg gcctgcccta ctgccaaaga ggtgacagga aggctgggag 180
cagctttgtt aaattgtgtt cagttctgtt acacagtgca ttgccctttg ttgggggtat 240
gcatgtatga acacacatgc ttgtcggaac gctttctcgg cgtttgtccc ttggctctca 300
tctcccccat tcctgtgcct actttgcctg agttcttcta cccccgcagt tgccagccac 360
attgggagtc tgtttgttcc agtggggttg agctgtcttt gtcgtggaga tcttggaact 420
ttgcacatgt cactact 437

<210> 81
<211> 472
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(472)
<223> n = A,T,C or G

<400> 81
atattttant aatgcagagc tatagtctca attgttactt tataaggtgg ttttattaac 60
aaacccaaat cctggatttt cctgtctttg ctgtattttg aaaaacacgt gttgactcca 120
ttgttttaca tgtagcaaag tctgccatct gtgtctgctg tattataaac agataagcag 180
cctacaagat aactgtattt ataaaccact cttcaacagc tggctccagt gctggtttta 240
gaacaagaat gaagtcattt tggagtcttt catgtctaaa agatttaagt taaaaacaaa 300
gtgttacttg gaaggttagc ttctatcatt ctggatagat tacagatata ataaccatgt 360
tgactatggg ggagagacgc tgcattccag aaacgtctta acacttgagt gaatcttcaa 420
aggaccctga cattaaatgc tgaggcttta atacacacat attttatccc aa 472

<210> 82
<211> 448
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(448)
<223> n = A,T,C or G

<400> 82
gttcagtgnt gccctcagag ctcttgctgt tagctggcag ctgacgctgc taggatagtt 60

agtttggaaa tggtacttca taataaacta cacaaggaaa gtcagccacc gtgtcttatg 120
aggaattgga cctaataaat tttagtgtgc cttccaaacc tgagaatata tgcttttgga 180
agttaaaatt taaatggctt ttgccacata catagatctt catgatgtgt gagtgtaatt 240
ccatgtggat atcagttacc aaacattaca aaaaaatttt atggcccaaa atgaccaacg 300
aaattgttac aatagaattt atccaatttt gatcttttta tattcttcta ccacacctgg 360
aaacagacca atagacattt tggggtttta taatgggcat ttgtataaag cattactctt 420
tttcaataaa ttgtttttta atttaaaa 448

<210> 83
<211> 270
<212> DNA
<213> Homo sapien

<400> 83
cagtgtggtg gaattaatca ggcctcccaa atttagcagg tgctggggag gaccctaggg 60
agtggtttat gggggctagc tggtgaaact gccctttcct ttctgttcta tgagtgtgat 120
ggtgtttgag aaaatgtggg gctatggttc aggcgcactt cacatgtgca aagatggaga 180
aagcactcac ctacacgttt aggctcagaa tattgattga aacattttga atgatcaaaa 240
ataaaatgtt atttttaaag tttcaaaaaa 270

<210> 84
<211> 359
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(359)
<223> n = A,T,C or G

<400> 84
tccaaagtta gacaaaatgc caggaatgtt cttctctgct aacccaaagg aattgaaagg 60
aaccactcat tcacttctag acgacaaaat gcaaaaaagg aggccaaaga cttttggaat 120
ggatatgaaa gcatacctga gatctatgat cccacatctg gaatctggaa tgaaatcttc 180
caagtccaag gatgtacttt ctgctgctga agtaatgcaa tggtctcaat ctctggaaaa 240
acttcttgcc aaccaaactg gtcaaaatgt ctttggaagt ttcctaaant ctgaattcag 300
tgaggagaat attgagttct ggctggcttg tgaanactat aagaaaacag agtctgatc 359

<210> 85
<211> 371
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(371)
<223> n = A,T,C or G

<400> 85
ctgcagcccg ggggatccac tagtccnttg tggtggaatt cagcctacag ccgcctgggt 60
ctgtatccag cgccaggtcc cgccagtccc agctgcgcgc gccccccagt cccgcacccg 120
ttcggcccag gctaagttag ccctcaccat gccggtcaaa ggaggcacca agtgcatcaa 180
atacctgctg ttcggattta acttcatctt ctggcttgcc gggattgctg tccttgccat 240
tggactatgg ctccgattcg actctcagac caagagcatc ttcgagcaag aaactaataa 300
taataattcc agcttctaca caggagtcta tattctgata cggagccggc gccctcatga 360
tgcttggtgg g 371

<210> 86
<211> 500

<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(500)
<223> n = A,T,C or G

<400> 86
ctgcagcccg ggggatccac tagtttncta tgatcattaa actcattctc agggttaaga 60
aaggaatgta aatttctgcc tcaatttgta cttcatcaat aagtttttga agagtgcaga 120
tttttagtca ggtcttaaaa ataaactcac aaatctggat gcatttctaa attctgcaaa 180
tgtttcctgg ggtgacttaa caaggaataa tcccacaata tacctagcta cctaatacat 240
ggagctgggg ctcaacccac tgtttttaag gatttgcgct aacttggggc tgaggaaaaa 300
taagtagtnc gaggaagtag tttttaaatg tgagcttata gatanaaaca gaatatcaac 360
ttaattatga aattgttaga acctgttctc ttgtatctga atctgattgc aattactatt 420
gtactgatag actccagcca ttgcaagtct cagatatctt agctgtgtag tgattcttga 480
aattcttttt aagaaaaatt 500

<210> 87
<211> 550
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(550)
<223> n = A,T,C or G

<400> 87
ctgcagcccg ggggatccac tagtccantg tggtggaatt ccaggaactg gaccaggnnc 60
tggagcggat ctccaccatg cgccttccgg atgagcgggg ccctctggag cacctctact 120
ccctgcacat ccccaactgt gacaagcatg gcctgtacaa cctcaaacag tgcaagatgt 180
ctctgaacgg gcagcgtggg gagtgctggt gtgtgaaccc caacaccggg aagctgatcc 240
agggagcccc caccatccgg ggggaccccg agtgtcatct cttctacaat gagcagcagg 300
aggctcgcgg ggtgcacacc cagcggatgc agtagaccgc agccagccgg tgcctggcgc 360
ccctgccccc cgcccctctc caaacaccgg cagaaaacgg agagtgcttg ggtggtgggt 420
gctggaggat tttccagttc tgacacacgt atttatattt ggaaagagac cagcaccgag 480
ctcggcacct ccccggcctc tctcttccca ngctgcagat gccacacctg ctccttcttg 540
ctttccccgg 550

<210> 88
<211> 429
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(429)
<223> n = A,T,C or G

<400> 88
gggaccagac tcgtctcagg ccanttgcag ccttctcagc caaacgccga ccaaggaaaa 60
ctcactacca tgagaattgc agtgatttgc ttttgcctcc taggcatcac ctgtgccata 120
ccagttaaac aggctgattc tggaagttct gaggaaaagc agctttacaa caaataccca 180
gatgctgtgg ccacatggct aaaccctgac ccatctcaga agcagaatct cctagcccca 240
cagaatgctg tgtcctctga agaaaccaat gactttaaac aagagaccct tccaagtaag 300
tccaacnaaa gccatgacca catggatgat atggatgatg aagatgatga tgaccatgtg 360
gacagccagg actccattga ctcgaacnac tctgatgatg tanatgacac tgatgattct 420

caccagtct 429

<210> 89
<211> 477
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(477)
<223> n = A,T,C or G

<400> 89
ttttaattta caccaagaac ttctcaataa aagaaaatca tgaatgctcc acaatttcaa 60
cataccacaa gagaagttaa tttcttaaca ttgtgttcta tgattatttg taagaccttc 120
accaagttct gatatctttt aaagacatag ttcaaaattg cttttgaaaa tctgtattct 180
tgaaaatatc cttgttgtgt attaggtttt taaataccag ctaaaggatt acctcactga 240
gtcatcaggt accctcctat tcagctcccc aagatgatgt gtttttgctt accctaagag 300
aggntttctt cttattttta gataattcaa gngcttagat aaattatgtt ttctttaagt 360
gtttatggta aactctttta aagaaaattt aatatgttat agctgaatct ttttggtaac 420
tttaaatctt tatcatagac tctgtacata tgttcaaatt agctgcttgc ctgatgt 477

<210> 90
<211> 310
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(310)
<223> n = A,T,C or G

<400> 90
ctgcagcccg ggggatccac tagtcanttt attgacacta tttgaaactt ttgaaatata 60
aacggagagg ctttctgttg agacattgtc accaaaacaa ttttttgaaa tgttcctgaa 120
actaatttgg gtttaaagat taaaagggtt gttaccattc ttatctgagt agttgggagg 180
aggggaatac cactttagtt catttggaaa atatagacat atttcttttg ctttcttaaa 240
acagcttaaa atgatgaact tttataattt taatttgaag attgaataaa tatttttttat 300
aaagataaaa 310

<210> 91
<211> 532
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(532)
<223> n = A,T,C or G

<400> 91
ctgcagcccg ggggatccac tagtcatgat gtgtgttgta ttttaaaaat tatctgcaac 60
cttaattcag ctgaagtact ttatatttca aaagaatgaa taacattgat aataaaatcg 120
ctactttaag gggtttgtcc aaaataaata ttgtggcctt atatatcaca ctattgtaga 180
aagtattatt taatttaaat ggatgcaggt tgtctactaa agaaagatta tatataacta 240
tgctaattgt tcataatcaa cagaaaccaa gatagagcta caaactcagc tgtacagttc 300
gtacactaaa ctcttcttgc ttttgcatta taaggaatta agtctccgat tattaggtga 360
tcaccctgga tgatcagttt tctgctgaag gcacctactc agtatctttt cctctttatc 420
actctgcatt ggtgaattta atcctctcct ttgtgttcaa cttttgtgtg cttttaaaat 480

cagctttatt ctaaagcaaa tctgtgtcta ctttaaaaaa ctgnaaatgg aa 532

<210> 92
<211> 608
<212> DNA
<213> Homo sapien

<400> 92
cactactgtc ttctccttgt agctaatcaa tcaatattct tcccttgcct gtgggcagtg 60
gagagtgctg ctgggtgtac gctgcacctg cccactgagt tggggaaaga ggataatcag 120
tgagcactgt tctgctcaga gctcctgatc taccccaccc cctaggatcc aggactgggt 180
caaagctgca tgaaaccagg ccctggcagc aacctgggaa tggctggagg tgggagagaa 240
cctgacttct ctttcccctct ccctcctcca acattactgg aactctatcc tgttaggatc 300
ttctgagctt gtttccctgc tgggtgggac agaggacaaa ggagaaggga gggtctagaa 360
gaggcagccc ttctttgtcc tctggggtaa atgagcttga cctagagtaa atggagagac 420
caaaagcctc tgatttttaa tttccataaa atgttagaag tatatatata catatatata 480
tttctttaaa tttttgagtc tttgatatgt ctaaaaatcc attccctctg ccctgaagcc 540
tgagtgagac acatgaagaa aactgtgttt catttaaaga tgttaattaa atgattgaaa 600
cttgaaaa 608

<210> 93
<211> 519
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(519)
<223> n = A,T,C or G

<400> 93
ctgcagcccg ggggatccac tagtccagtg tggtggaatt ctaaagaagt aggtgctgca 60
cacaaatatg taaagcaatt gtaggaaatt tgaaaggaaa aaaagaaacc gaagccagta 120
ttttaataat tgctttttct gtgtattttg tattgggctg ggggatagca tcaaaggttg 180
aacttttga gctttctatg aaaaacccca ggaccttctt tctttggcca tttctatgga 240
aatgcgatgt cagatggatg gtaatggtgc cctccagtgg ctgtgagacc tcattgcgca 300
ttgtctactg gagctttagt cttctgagac ggaggaaaac tgctgaatac tctggattca 360
tctatgtcta caatgttgca tttatgaaaa actacactgn gctaggcgca ttctaggaca 420
tgaatatgac cacaccctct ttcaccgggt gtttctgtag caagttttca tattcttttc 480
aaacaatggt ttctctgcgt taattattga ggaaaaaaa 519

<210> 94
<211> 569
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(569)
<223> n = A,T,C or G

<400> 94
ctgcagcccg ggggatccac tagtccantg tggtggaatt cgtctgcgag ccaggattcc 60
cgatccagag acaatggccc cgatgggatg gagcccgaag gcgtcatcga gagtaactgg 120
aatgagattg ttgacagctt tgatgacatg aacctctcgg agtcccttct ccgtggcatc 180
tacgcctatg gttttgagaa gccctctgcc atccagcagc gagccattct accttgtatc 240
aagggttatg atgtgattgc tcaagcccaa tctgggactg ggaaaacggc cacatttgcc 300
atatcgattc tgcagcagat tgaattagat ctnaaagcca cccaggcctt ggtcctagca 360
cccactcgag aattggctca gcagatacag aaggtggtcn tggcactagg agactacatg 420

ggcgcctcct gtcacgcctg tatcgggggc accaacgtgc gtgctgaggt gcagaaactg 480
cagatggaag ctccccacat catcgtgggt acccctggcc gtgtgtttga tatgcttaac 540
cggagatacc tgtcccccaa atacatcaa 569

<210> 95
<211> 260
<212> DNA
<213> Homo sapien

<400> 95
gacaagctcc tggtcttgag atgtcttctc gttaaggaga tgggcctttt ggaggtaaag 60
gataaaatga atgagttctg tcatgattca ctattctaga acttgcatga cctttactgt 120
gttagctctt tgaatgttct tgaaatttta gactttcttt gtaaacaaat gatatgtcct 180
tatcattgta taaaagctgt tatgtgcaac agtgtggaga ttccttgtct gatttaataa 240
aatacttaaa cactgaaaaa 260

<210> 96
<211> 438
<212> DNA
<213> Homo sapien

<400> 96
atttctcttt agttctttgc aagaaggtag agataaagac acttttttcaa aaatggcaat 60
ggtatcagaa ttcctcaagc aggcctggtt tattgaaaat gaagagcagg aatatgttca 120
aactgtgaag tcatccaaag gtggtcccgg atcagcggtg agcccctatc ctaccttcaa 180
tccatcctcg gatgtcgctg ccttgcataa ggccataatg gttaaaggtg tggatgaagc 240
aaccatcatt gacattctaa ctaagcgaaa caatgcacag cgtcaacaga tcaaagcagc 300
atatctccag gaaacaggaa agcccctgga tgaaacactg aagaaagccc ttacaggtca 360
ccttgaggag gttgttttag ctctgctaaa aactccggcg caatttgatg ctgatgaact 420
tcgttgctgc catgaagg 438

<210> 97
<211> 471
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(471)
<223> n = A,T,C or G

<400> 97
tcgttatccg cgatgngttt cctggcagct acattcctgc tcctggcgct cagcaccgct 60
gcccaggccg aaccggtgca gttcaaggac tgcgatattc agtctaaaag cagcaaggcc 120
gtggtgcatg gcatcctgat gggcgtccca gttccctttc ccattcctga gcctgatggt 180
tgtaagagtg gaattaactg ccctatccaa aaagacaaga cctatagcta cctgaataaa 240
ctaccagtga aaagcgaata tccctctata aaactggtgg tggagtggca acttcaggat 300
gacaaaaacc aaagtctctt ctgctgggaa atcccagtac agatcgtttc tcatctctaa 360
gtgcctcatt gagttcggtg catctggcca atgagtctgc tgagactctt gacagcacct 420
ccagctctgc tgcttcaaca acagtgactt gctctccaat ggtatccagt g 471

<210> 98
<211> 578
<212> DNA
<213> Homo sapien

<400> 98
ccagtgtggt ggaattcgca gccaccgcca cccattggaa tggccaacag gggacctgca 60
tatggcctga gccgggaggt gcagcagaag attgagaaac aatatgatgc agatctggag 120

cagatcctga tccagtggat caccacccag tgccgaaagg atgtgggccg gccccagcct 180
ggacgcgaga acttccagaa ctggctcaag gatggcacgg tgctatgtga gctcattaat 240
gcactgtacc ccgaggggca ggccccagta aagaagatcc aggcctccac catggccttc 300
aagcagatgg agcagatctc tcagttcctg caagcagctg agcgctatgg cattaacacc 360
actgacatct tccaaactgt ggacctctgg gaaggaaaga acatggcctg tgtgcagcgg 420
acgctgatga atctgggtgg gctggcagta gcccgagatg atgggctctt ctctggggat 480
cccaactggt tccctaagaa atccaaggag aatcctcgga acttctcgga taaccagctg 540
caagagggca agaacgtgat cgggttacag atgggcac 578

<210> 99
<211> 416
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(416)
<223> n = A,T,C or G

<400> 99
caagaatgtg cctaactggc atanagatct ggtacgagtg tgtgaaaaca tccccattgt 60
gntgngtggc aacaaagtgg atattaagga caggaaagtg aaggcgaaat ccattgtctt 120
ccaccgaaag aagaatcttc agtactacga catttctgcc aaaagtaact acaactttga 180
aaagcccttc ctctggcttg ctaggaagct cattggagac cctaacttgg aatttgttgc 240
catgcctgct ctcgccccac cagaagttgt catggaccca gctttggcag cacagtatga 300
gcacgactta gaggttgctc anacaactgc tctcccggat gaggatgatg acctgtgaga 360
atgaagctgg agcccancgn cagaagtcta gttttatang cagctgtcct gtgatg 416

<210> 100
<211> 441
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(441)
<223> n = A,T,C or G

<400> 100
agacaatgac cccacggntc ctccttatga ctccattcaa atctacggtt atgaaggcag 60
gggctcagtg gccgggtccc tgagctccct agagtcggcc accacagatt cagacttgga 120
ctatgattat ctacagaact ggggacctcg ttttaagaaa ctagcagatt tgtatggttc 180
caaagacact tttgatgacg attcttaaca ataacgatac aaatttggcc ttaagaactg 240
tgtctggcgt tctcaagaat ctanaagatg tgtaaacagg tatttttta aatcaaggaa 300
aggctcattt aaaacaggca aagttttaca gagaggatac atttaataaa actgcgagga 360
catcaaagtg gtaaatactg tgaaatacct tttctcacaa aaaggcaaat attgaagttg 420
tttatcaact tcgctagaaa a 441

<210> 101
<211> 521
<212> DNA
<213> Homo sapien

<400> 101
ccagcgccca gagagacacc agagaaccca ccatggcccc ctttgagccc ctggcttctg 60
gcatcctgtt gttgctgtgg ctgatagccc ccagcagggc ctgcacctgt gtcccacccc 120
acccacagac ggccttctgc aattccgacc tcgtcatcag ggccaagttc gtggggacac 180
cagaagtcaa ccagaccacc ttataccagc gttatgagat caagatgacc aagatgtata 240
aagggttcca agccttaggg gatgccgctg acatccggtt cgtctacacc cccgccatgg 300

agagtgtctg cggatacttc cacaggtccc acaaccgcag cgaggagttt ctcattgctg 360
gaaaactgca ggatggactc ttgcacatca ctacctgcag tttcgtggct ccctggaaca 420
gcctgagctt agctcagcgc cggggcttca ccaagaccta cactgttggc tgtgaggaat 480
gcacagtgtt tccctgttta tccatcccct gcaaactgca g 521

<210> 102
<211> 520
<212> DNA
<213> Homo sapien

<400> 102
gaagaaaaag aaattctgat acgggacaaa aatgctcttc aaaacatcat tctttatcac 60
ctgacaccag gagttttcat tggaaaagga tttgaacctg gtgttactaa cattttaaag 120
accacacaag gaagcaaaat ctttctgaaa gaagtaaatg atacacttct ggtgaatgaa 180
ttgaaatcaa aagaatctga catcatgaca acaaatggtg taattcatgt tgtagataaa 240
ctcctctatc cagcagacac acctgttgga aatgatcaac tgctggaaat acttaataaa 300
ttaatcaaat acatccaaat taagtttgtt cgtggtagca ccttcaaaga aatccccgtg 360
actgtctata gacccacact aacaaaagtc aaaattgaag gtgaacctga attcagactg 420
attaaagaag gtgaaacaat aactgaagtg atccatggag agccaattat taaaaaatac 480
accaaaatca ttgatggagt gcctgtggaa ataactgaaa 520

<210> 103
<211> 479
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(479)
<223> n = A,T,C or G

<400> 103
ctgattctca ggctagaagt gtcacttttc ttatctgtac ttccaaagca ctttcgtata 60
tttttattat ggcatttata tatagttcat ttatatttaa attttaattc catgaacaat 120
caagtaccaa gtataatgga gaaggtgctc atcctctgcc ttccttgagc ttctgggtga 180
tgccaggccc aagtctttgt ggcacccagc tccatgcttt gaatactatg tggctgaatg 240
aatttttaaa atctcaaagc agttaaacag caggaaagcc cattaacttc gtactgaaaa 300
agcaacatac tgtgatgata cgggatgaca tcatttcagg ttgggcatac aaaaaagtaa 360
ggaagctaaa ctaagactat actcaccagg ccatttagaa gttttaaata atgcctccac 420
tatttttttt cttanacata gcttttaatg gggaaatgga attagtaaat gactatttt 479

<210> 104
<211> 324
<212> DNA
<213> Homo sapien

<400> 104
tgaccatcca tatccaatgt tctcatttaa acattaccca gcatcattgt ttataatcag 60
aaactctggt ccttctgtct ggtggcactt agagtctttt gtgccataat gcagcagtat 120
ggagggagga ttttatggag aaatggggat agtcttcatg accacaaata aataaaggaa 180
aactaagctg cattgtgggt tttgaaaagg ttattatact tcttaacaat tctttttttc 240
agggactttt ctagctgtat gactgttact tgaccttctt tgaaaagcat tcccaaaatg 300
ctctatttta gatagattaa catt 324

<210> 105
<211> 541
<212> DNA
<213> Homo sapien

<400> 105
cttggttcca gaacctgacg acccggcgac ggcgacgtct cttttgacta aaagacagtg 60
tccagtgctc cagcctagga gtctacgggg accgcctccc gcgccgccac catgcccaac 120
ttctctggca actggaaaat catccgatcg gaaaacttcg aggaattgct caaagtgctg 180
ggggtgaatg tgatgctgag gaagattgct gtggctgcag cgtccaagcc agcagtggag 240
atcaaacagg agggagacac tttctacatc aaaacctcca ccaccgtgcg caccacagag 300
attaacttca aggttgggga ggagtttgag gagcagactg tggatgggag gccctgtaag 360
agcctggtga aatgggagag tgagaataaa atggtctgtg agcagaagct cctgaaggga 420
gagggcccca agacctcgtg gaccagagaa ctgaccaacg atggggaact gatcctgacc 480
atgacggcgg atgacgttgt gtgcaccagg gtctacgtcc gagagtgagt ggccacaggt 540
a 541

<210> 106
<211> 391
<212> DNA
<213> Homo sapien

<400> 106
cagaagtctt ggactgcaac tacatacatg gaatatgaga ctcttaccct gggagatatg 60
attaggagaa gtggtggcca cagtcgaaaa atcccaaggc ccaaacctgc accactgact 120
gctgaaatac agcaaaagat tttgcatttg ccaacatctt gggactggag aaatgttcat 180
ggtatcaatt ttgtcagtcc tgttcgaaac caagcatcct gtggcagctg ctactcattt 240
gcttctatgg gtatgctaga agcgagaatc cgtatactaa ccaacaattc tcagacccca 300
atcctaagcc ctcaggaggt tgtgtcttgt agccagtatg ctcaaggctg tgaaggcggc 360
ttcccatacc ttattgcagg aaagtacgcc c 391

<210> 107
<211> 462
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(462)
<223> n = A,T,C or G

<400> 107
cgtgacctca agatgngcca ctctgactgg aagagtggag agtactggat tgaccccaac 60
caaggctgca acctggatgc catcaaagtc ttctgcaaca tggagactgg tgagacctgc 120
gtgtacccca ctcagcccag tgtggcccag aagaactggt acatcagcaa gaaccccaag 180
gacaagaggc atgtctggtt cggcgagagc atgaccgatg gattccagtt cgagtatggc 240
ggccagggct ccgaccctgc cgatgtggcc atccagctga ccttcctgcg cctgatgtcc 300
accgaggcct cccagaacat cacctaccac tgcaagaaca gcgtggccta catggaccag 360
cagactgggn acctcaataa ggccctgctc ctccagggct ccaacganat ngagatccgc 420
gccgagggca acagccgctt cacctacagc gtcactgtcg at 462

<210> 108
<211> 580
<212> DNA
<213> Homo sapien

<400> 108
atataccatt taatacattt acactttctt atttaagaag atattgaatg caaaataatt 60
gacatataga actttacaaa catatgtcca aggactctaa attgagactc ttccacatgt 120
acaatctcat catcctgaag cctataatga agaaaaagat ctagaaactg agttgtggag 180
ctgactctaa tcaaatgtga tgattggaat tagaccattt ggcctttgaa ctttcatagg 240
aaaaatgacc caacatttct tagcatgagc tacctcatct ctagaagctg ggatggactt 300
actattcttg tttatatttt agatactgaa aggtgctatg cttctgttat tattccaaga 360
ctggagatag gcagggctaa aaaggtatta ttatttttcc tttaatgatg gtgctaaaat 420

tcttcctata aaattcctta aaaataaaga tggtttaatc actaccattg tgaaaacata 480
actgttagac ttcccgtttc tgaaagaaag agcatcgttc caatgcttgt tcactgttcc 540
tctgtcatac tgtatctgga atgctttgta atacttgcat 580

<210> 109
<211> 482
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(482)
<223> n = A,T,C or G

<400> 109
caggcgtgca gtttcccggc tctccgcgcg gccggggaag gtcagcgccg taatggcgtt 60
cttggcgtcg ggaccctacc tgacccatca gcaaaaggtg ttgcggcttt ataagcgggc 120
gctacgccac ctcgagtcgt ggtgcgtcca gagagacaaa taccgatact ttgcttgttt 180
gatgagagcc cggtttgaag aacataagaa tgaaaaggat atggcgaagg ccacccagct 240
gctgaaggag gccgaggaag aattctggta ccgtcagcat ccacagccat acatcttccc 300
tgactctcct gggggcacct cctatgagag atacnattgc tacaaggtcc cagaatggtg 360
cttagatgac tggcatcctt ctgagaaggc aatgtatcct gattactttg ccaagagaga 420
acagtggaag aaactgcgga gggaaagctg ggaacgagag gttaagcagc tgcaggagga 480
aa 482

<210> 110
<211> 286
<212> DNA
<213> Homo sapien

<400> 110
aatcattctg cactcactgg gtgcatagca tggttagagg ggctagagat ggacagtcat 60
caactggcgg atatagcggt acatatgatc cttagccacc agggcacaag cttaccagta 120
gacaatacag acagagcttt tgttgagctg taactgagct atggaatagc ttctttgatg 180
tacctctttg ccttaaattg ctttttagtt ctaagattgt agaatgatcc tttcaaattg 240
taatcttttc taacagagat attttaatat acttgctttc ttaaaa 286

<210> 111
<211> 465
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(465)
<223> n = A,T,C or G

<400> 111
agctactgtt aagatttgac agattgtctt gtctttttcc agtatatata ggtatctata 60
tatgtatata ctgtatatac ttatatatat ttattgtatt aaatatatac atatgtatat 120
gtatatataa gtatgtgtat atatgtatat atttaataca attattaaat tgtattattg 180
tattaaatgt atacatatat acacacatat atatacatat gcatatattt aacacagtta 240
aaataacact aaatgtacca ttttgtttct ggccttttca gntaatgtta tgaagaattt 300
ttctattttg ttaaacttct ccaaaaacat taaactgcat tatgttctga gagtagatgt 360
accacaatta attctaccat ttctgtattg ttggccatgt aggttgttct taattttctc 420
attattatga atgcatgtga caatcattgg ttttgcctaa agttg 465

<210> 112
<211> 773

<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(773)
<223> n = A,T,C or G

<400> 112
tttttttca gtttttgcag ttggtgtggt tagcagatac tttcttagaa taaaattgat 60
aactcaattt gatttttaaa aagttgtttt agtgatttaa aatgttgata tggaaaaata 120
ttaaacatta tatagatagt aggcaaattc atatcctaat tgcaatatta gcttgtagca 180
ttttaaatta aaatctaaat ttcttgatat attgccacat tagttgtaat gtttaataaa 240
tggtggttaa agatttattt gtaatttaat ctgtgtactt agttgccatg gacctctctt 300
ttagcttttc ataaataaat atcctttaat accttacctc ctcccttcaa ttgactgatg 360
ctgggatagg gtgttctttg gagcttatct tggtaaagaa ggtcagaagt gacatataac 420
cctattccct aggggccgag ggtgctttcc ttacagagtt gtattttaag tgagtcaact 480
cctgagccag catctactaa gagaaccttc aaacataatc ataggcattt aaataatttg 540
aaaaatcaaa ttccttgcat taaaaacatt tatccttang ttcatttctt tataanggtt 600
ctctttttaa aaaaaaggat tggtatttat gaaagggaat ggtggctggg tttttcttaa 660
gcattatgna aagggggagt acccctattt ttctttctcc ccanggaaaa tgggtgaagg 720
gaacctgggc aatgcccatg attgnaaaaa ttccactttc nttgaacaat ggg 773

<210> 113
<211> 543
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(543)
<223> n = A,T,C or G

<400> 113
gtttttctga tttgaaaaat tgtttataat attactataa gatgagatta acaatctttg 60
taaaaatcag attatgtttt gggcttaaaa aaaaccctag tgttttctac tattagtgta 120
ctcaaatgat ttgtgagtga tagtactcaa atgagaattg catttaattt gtacatagtt 180
aaatcgtctt gttttgaagc acaaagtcag gatgtttctc atcagaattt tctgtttgaa 240
tagggaaaag tggcattggt catgaggcat cattaaaaac ggaaagcaga ggaaaaattg 300
gaaagctaca gaaaaaagat tcacatgaaa aaccaagctg aagaaaaaag ctgcagaaca 360
gtttcgaatg cgacttaaaa aattaagcca agatgnaaat gaagctagaa agggagatct 420
cagaaagaag ccagccgagc ctgtcaaaca actggatgtc cagaaaaata ttcaggttcc 480
ccaggggaaa gcatgggtac tgggtttgan gcttggaaga nggagactgg aaggaaagaa 540
tga 543

<210> 114
<211> 550
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(550)
<223> n = A,T,C or G

<400> 114
ggaaagaggt aagcggtaaa ttacatagac tgctggagga agagtgttcc agtggagaga 60
aacagagcta gtgcaaaggc cctgaggtga gagcatgcct ggtgtgatcc ggggatggca 120
aggaggccag ggtggtggat gaggagttag caaggaggan agtacgagga taagaagcca 180

ncaaggaaaa atggcagtgg ggcggatcac ctangggtct agtacgccat tgtgaagact 240
ttgccttttg ctcccaantg gaatgggtac tcnttgaagg cttttaancc caggaanaaa 300
cattgattga tttanaagtt taaanggatc acntttgggt attgtggcca acaagacact 360
gcgggaagaa gcaagaaggg tagaaagcca gnaaaccaac tnaggaggct tttgcagtaa 420
tcctggntga nanacantgg tggtctnggt taaaaagttt tggaaaaaat taaaactgtt 480
tgatggtttg tttcctgttc ttgggggcnt aggcattcca actccttacc gaaagggtta 540
ccccntttga 550

<210> 115
<211> 550
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(550)
<223> n = A,T,C or G

<400> 115
caatgtggca cttaacttan tgggtacaac tgtatcacat catgtgtgaa tcgtgagacc 60
actcaaatct ctctctggga aaacncggct gctcccccga tggctggcag gtgttggaac 120
ctcggtctcc cgtccgtctc tggggcaagg tgggtttcct catgtatngc aagagtctat 180
cgtgcggtgc ttctctcttg gcatacagct cacagctctt tggcctatac agtgtggaaa 240
tttatnctcc ggtgctggag gtgttaatgg gaaagagctc ggttaaatgc acttctcact 300
tggcccgtgg gtgatgctct acatgactga attcntctct nacggggact gacattgtat 360
ctatacacta natccttcca ccanagtggc gttaaggacg gtgtctggga tggaanctga 420
cggtacangc cccanctctc tgaaatgagt ccananatga actacctgca tacctctcta 480
aatcactctg gtctggcatg ntctccgtgc cgaaacatat atatgtatgt ctctccncat 540
acgaaaanaa 550

<210> 116
<211> 463
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(463)
<223> n = A,T,C or G

<400> 116
cacaatgtgg tactttactt agttggtaca actgtatcat atcatgtggt gaatcacgtg 60
tgacgtgact ccgcaactcc gcaccagact acactgcacg taatnacagc cngcacncca 120
ggtggacaaa nattgacgca atgttgtgtc antgccaccg tgccacacca cctgtggagg 180
acgtcagtct tctcttcccc caaaacccag gaccctcntg atctcccgac cngaggtcct 240
nggttgtggt gactgagcnc aaaaccgagg tcgttcactg gtacttgacg ctggagtcat 300
atccaganaa agcccggaag acatcacngc cttcgtgtgt cnctctcacg tctgcacaga 360
cggctaacgc aggatcattc angtccacaa gctccacccc tcanaaactc tcnaacaagg 420
cagccgaaac acgtttccct gccctccgga gaatacanaa cag 463

<210> 117
<211> 503
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(503)
<223> n = A,T,C or G

<400> 117
nncactnatg tgctacgtta acttagttgt acaactcgat cctatccatg tggtgaattc 60
tctccagcag tacactgang atacanctta ttgttattga cgtgcgctgc gctcactacc 120
gncagccagg gaatgcgcct caggaaccct ggtgcccacc ctggctggca tngccattgt 180
caaggaagag aaacgagntg ccattggagc cctcctactg ccatgagggc ctgaaacaaa 240
ctgtgntatg ctctgcgaag gtctggtgct aaggtcccgc tggctcacta tggcacacca 300
ctcngggctg aagttgtggt cctgaaggta ctcancccag tgtggccggg acctggatac 360
gtgcacattg ccgtgtcgca aaaccagcat tgtatgtgca catgtagttt gttccactga 420
atgtcnctgc ggcctcagat ttcagggaga ttgactctca tctcnttgtc ctactaagag 480
agagcacctc acctgaatgt caa 503

<210> 118
<211> 560
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(560)
<223> n = A,T,C or G

<400> 118
tgggggnnca ctaagtgcta cgttacttag ttgtacgact cgatcctatc atgtggtgaa 60
ttctgnagcn tggtctcatg agcctctctg gtgcgctgtg tgtatnggta cggcgctctc 120
tatcgcttta tctcttctga ctcgcaccgg ggccggcggc atcaccggcc aagaccctgc 180
acaatgaaga ctgcaggagc aggcgggtgg cccacctggc cctggacctg aagaccnaaa 240
ctggagcagg ctcgngccgg aggactgggc accgcctaca ggccacgtca cccacggtgg 300
ctggnanaac aatgaaaaca agaagaactt ctctacccaa gagagaagtt caaaaccncg 360
aactcactgt cgggaaattg actaaaactg cngaactgaa gaaaacaacn caaagccnnc 420
tnaagcanag aagngaactg agacgaacat catccnccna actaatgaaa agagagacgt 480
tccctgnaga gacnaagaga gagaaagagc cccagacngc cccggactaa gattctaata 540
agagcttgtt gtgagagaag 560

<210> 119
<211> 638
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(638)
<223> n = A,T,C or G

<400> 119
acaaaagtgc tacgttactt agctgtacga ctcgtcatat ccatgtggtg aatcatacgc 60
tattttatat acngtngatc aacatgaagg gttngtgtct gatcccgcgc atcaaaacac 120
gtgttacttt gactccccaa acctactcta gtaataccta ctattgacca gaaccttaca 180
ttacataaac agttnccata ttctgtatat atatgtatac tgtattctta ataagtaagc 240
taagaaatgt tattgaaatc ataaggaaaa gaaatgtatt atacactgta tgtattgtct 300
gtantgtact gtctgttaca agatgatcgt ctgatgaatg atgcgctgca ccccaactat 360
gtattacaaa caatcncttt tcattgtgtc tgacttgctt ctgaaatact ccacacncta 420
tngctttata tggtcctggt gtattcaggt tatntatgcc taactgaaaa tcccagaacc 480
tgaagatatg tttctgtgat cncattactg ganaaagaac gcccatcaat actcnccgng 540
tttaacggat ccccacctga cnccgcatac acagagtgta naatttgtnt acacttntca 600
cgtanctagc tttgaataac gctcttcttt ttcttccc 638

<210> 120
<211> 434

<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(434)
<223> n = A,T,C or G

<400> 120
ngnnggggca caaaagctgc tatgtttaac ttagcttggg tacgactcgt tcatatccat 60
gtgnttgant caccgctcta ctgccaagca tcattttggt tctacgnctc aanctgtgna 120
aangatgtgg gttaggggan tgaagatgca aacncctagg gtangggcat ttanaactga 180
aaagganagg aaganaagac ctgcgaacgt gggggataag actanaagaa agacgggaga 240
naatantgtc tttgancctc aaatggaaca tntcccatcc tatctgttan aaancaccan 300
gtaaaatggg atgtntgcac naaagaataa gttaaactaa acnccggacn gtgactanaa 360
aatgaangac cacanatgaa aaggcgatga ctngcctgtt tacctancct gtanacctat 420
attttcnggg ttat 434

<210> 121
<211> 631
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(631)
<223> n = A,T,C or G

<400> 121
caaagcgcta tgttaatgag cttgtacgac tcgtcatatc ttgtggtgta tcatattctc 60
tctctctttc aacaaactcc ccagctccac ccgggctcta cctccgagac cagganccaa 120
aacgancgaa gatggctgct ctgcgcgcca cgccgcgcca ctcccgctgc ccccggcccc 180
gattccttgg ataaaganaa gaatcgcaag aaaccatcaa tcgcactctc cttctccggc 240
gctcgncgtt ccggctccgg gtcggatgct gcaaatgctg ggatgccgag ntgtgcgcgg 300
gcccagntgc gcacggttac acacaccact ctggactgga gaagaatcat ttatanttct 360
gtgccgcacc cgcgtcaaat gcgcttgctg aactcacgaa agnagtcaat ntgttctaac 420
gngctgaaca cacgcagacc ncacnaaagc gccgatggga ctgctgccgg aacctggaga 480
ctctcaactc caagaaccgc gcaaccgggc ggcctccgct ccggcgntgg gaactgtntc 540
cccccgaagt tgttccggnt taacgcgacc cggttanctt cgtnaaaggg ngggcctnaa 600
ttcggtgcct tncnggcggg gggtgaccgc c 631

<210> 122
<211> 678
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(678)
<223> n = A,T,C or G

<400> 122
caaagcggct angttaatta gctggtacga ctcgtcatat catgtggtgn atccacacat 60
ggaatgaggg tcccgctcac tctggggctc tgctgctctg gtccatgtgc cagatntaaa 120
tccagatgac cagtctcctc ctccctgtct gcatcggtgg ganacgaatc accatcactt 180
gncgggcaat caganattan aaatgattaa cctggtatca gcagaaacca gggaaaccct 240
aagctctgat ctttgctgca tcagttacaa gtggggtcct tcncgcttca cggcagtgnt 300
ctggcacaga ttcatctcac atcncagctg cagcctgaaa aatttacact tatactgtct 360
acggataaca ataccctgna cttcggcaag gactanggtg gaatnaaacn aatgtggctg 420

cacatctgtc ttctcttccc gctctgataa cagtnaaatc tgaactgctc tgttgtgtgc 480
tgctgatact tctatccana aaagccaagt acatggaagt gaatacgcct ccaatcggtt 540
atccagaaat gtccaaanag gaacaggacg nctacgctcg cacncctgac ctaaccancn 600
aatcnaaaac caatctnccc gcaatccctc gggctgaccc ctccaaaact ccngggaatt 660
taaggaaatc cccccccc 678

<210> 123
<211> 445
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(445)
<223> n = A,T,C or G

<400> 123
gagggggngg caaaagcgct acttaattag ctgtacgact cgtcatatca tgtggtggat 60
cagcatccag atggcataat cggctaatgt cctggggttc agatgtatgc gatgtccggc 120
taatgtgaca tcttgccanc tagcttaagg anggctggct agaagacatt gcagaaacag 180
gagctcggcc cacangtttc ccaaggctct caccccattc catctccagg gaagctcgcc 240
cagtggcact gaatggcctc ctcagcggag ggtttggaat caggctgggc aagaactgct 300
aatcttgcgc ggactggaac cagctctccg gccttctctg gctccttggt tctggtgggg 360
aagggaagag ggaaaagaaa ggaaatctcc nggcananga ngggacaccc canacaccga 420
agacacnccc ccctcctgta actgt 445

<210> 124
<211> 641
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(641)
<223> n = A,T,C or G

<400> 124
gagggggggg ncaaagcgct acgttaatta gctgtacgac tcgtcatatc atgtggtgga 60
tcccactaca angttgtcac tatatattan atctatagtn gagtcngtnt tccccatccc 120
tgtaaacgaa tttactattg ttggggtagt gtccctactt tcctgattaa ggatctgtgc 180
tggggaacaa gcnttgcata ccttatatgt agttaanatt tattaacata tcctcatgan 240
ctcattcaca ctgnanctct cctnaaaatn gtgtgctcct gttacattan aactaatctg 300
aaataaagac tctcnaatgc tgtgcaacat anttactgtn tgaaggagca gtgtnaattg 360
agtaccaatt tagcatcgat ttgaaacgca ccttatttga actgtgaata aacactttct 420
gcgtatacta ctgcttacat ccaattcngt gatttaagat actcgtggta tagatacact 480
gattgaagtc cgatatatgc aaaactcctt cataggattg acatgctgat ntnagtgngc 540
nttcaatgtg gagtatactt acntaattgc taacgtataa agtattgaan gtnnaatagt 600
cagcttcngt gnaaaatnng aaattagtat ggtncngttc c 641

<210> 125
<211> 285
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(285)
<223> n = A,T,C or G

<400> 125
aggggngcac aaagcgctac gttaatnagc tgtacgaccg tccatatcag gtggtggatc 60
catatgtccg gtattctctg atgtcangct tattataata gtaccaaccc ttcatctctg 120
aaatgtctgg ttctggttcc ctattatata ccagcactga aaatattcgt atcttagnan 180
caaaagcatt taaaaagagt taaaaattta ntcatcacta tgcacttcaa ggggagaagc 240
tncactgcnt ncttgagnct angcaagatg cnagcnccct ggaag 285

<210> 126
<211> 282
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(282)
<223> n = A,T,C or G

<400> 126
agggnntgac aaagcggcta cgttaatnag ctggtacgac cgtcatatcn tgtggtggat 60
ccngaacang tagcctcata atcacaacat ccattagcca cagtaaactg attctgtaac 120
tccactggca atgctgattg gtaatggctg cataaaccca gtgtatcaat ttantttcgg 180
ttttgagaca aaatctcata ttatacnctg acatctcnaa cttcgataca tgaccaaata 240
cgggnagaca ttattcaaan atatttacct tacanaaaaa aa 282

<210> 127
<211> 634
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(634)
<223> n = A,T,C or G

<400> 127
acaaagcggc tacgttantc agctggtacg accgtccata tcatgtggtg gatcntgaaa 60
ancttgatc ggctgcggtg gaaacgttgt cngggccggc aagaagagcc gctgtnacaa 120
tggtgtcatg agttcagccg aacgcangac ggttctcaca cccgtgctgc ggtgttgcca 180
tgtccgcacg ggacaatatc ctggggaccg gtactggtag taactatgat gcattntgct 240
gantgtgaat gatctcaact catgccagct gtcacattca tagaattctc gtaatatatc 300
ntcgaaaaat ggtaanatgc tgtgtctttt gccgtcctgt tctatgttta tatcagtcag 360
ctgttatgac attctatcag tggttggctg atccatctct gttacnactt tgactcgtct 420
cattgccgtt gctatagtcc tcactattgc cagatcaaaa tactgatcac tactaattcc 480
nacaananac tctggctgga ccactgcccn gtcatgtctg tgtcttgcta tcacatttaa 540
gctactatta ctgtgttgga atgcataatc tcacaacnaa gtgcgaaatg ngtttccgcc 600
ttgaatacnc cctactttgc ccctataaag gcgg 634

<210> 128
<211> 180
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(180)
<223> n = A,T,C or G

<400> 128
caaagcgcta cgttaatnag ctgtacgacc gtccatngtc aggtggtgga tccctgttat 60

gtcaagaaaa gtaaatcgtc tcttcaataa ggcctttatt tgggacaggt ttatttcctg 120
atatnatntc ttttatactc ttttctctca gaaanaaaaa agtngtntnc tcttattgtc 180

<210> 129
<211> 567
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(567)
<223> n = A,T,C or G

<400> 129
acaaagcgct atgttaactt agctgtacga ccgtccatng tcaggtggtg gatcctcccg 60
tgtgctggat tcataatgga tctatttaga cagttgagaa taaattattc tattacaata 120
atagatgcta atatatatat tatgctgttt ggatatctaa atatttgctc acatccttaa 180
tatattttta aaattctaac aatagtactg ttganataaa gttgagccat attganacnc 240
tcccanattg gtcctagaaa gttacactgg ttgtctctcc ttatgtcctg ttatccaccc 300
tgacgctgcc gctttatatt cttaatgant tggacggaca gtggtatccg atcgttttga 360
cgacgttaca ntactnacca tctatacgtc tacttaattg acagcagatt tcgtagcnct 420
cattaggatc tgttccaacn gttggcaaat naccncggan gaagttccng tagttgtcnn 480
ctccccctat tgaaacttat gaccnatctt cctttacnca catatcgacc ttcctgacaa 540
cncctttnn aaagaactct tcnccca 567

<210> 130
<211> 557
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(557)
<223> n = A,T,C or G

<400> 130
agggnntcac aaaagcgcta cgttaatnag ctgtacgact cgtcatatca tgtggtggat 60
cccgcggcgt gcggactgga tgtcaaactc tgcctgcggc gatgcgccga tcggcgcccg 120
ggatacgtgg caagcgcggg cccggcgcca gccgcactct cccancctgg cgtggccacc 180
cggccaagca gaatgggtcc tgcagctgcn gtctagcngt ctgcaccaac acgggtggtg 240
gtgcagcnaa gtctccggaa tccncaaggt ctattnaatt ctgtgggaaa ttanatctca 300
actcaatagg cctttccaaa gaactattgc atgatattca acaagtaatt tcttatttca 360
atacactccg tatcagaatc atgttctttc tcgatctctt ccatcctccg aacagcctgc 420
antgactgtt tcacctagac aannaataca tccttggtat tgggactcag cataactgtc 480
aaatatgcta tcnactccna tcnaagaaat ctttccgaag ctgtatttga ttcattaatt 540
tatccacatt actggat 557

<210> 131
<211> 655
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(655)
<223> n = A,T,C or G

<400> 131
agggnggcac aaagcgctat gttactgagc tgtacgnctc gtccattgtc ntgtggtgga 60

tcntcggatn aggtctgata tacttcctgt gngatcnaga tgnatctncg tagntccccc 120
cgttggatgc tgctcatnac tgctgcattt ccacgatcca ccctgtnatg gctatcctgc 180
tatacacaac ngcatgatnn gatatggaat cctccacaat ggaagtgttc tgttatgacc 240
caccacctta tatncngccg ctgtctgaaa ctcaaaccct ttgcctgtnt cagancacga 300
tcngttatgt tactgatgaa gaaatggaat actcccaaaa acagtgctcn gccgcaaatc 360
ctacttccng caaatcnact gcgtctctta atcctaactc ctctccatan aanctacagt 420
tactccgtga agccntgaag gaaatgggan agttatagga aactntcatc gttataagcc 480
anaatgcntg attaaataaa tcgtctttng tgataacctc atcttcactc ngttatacct 540
atcgttactn canaancctt attgaanttg aattgtnttg aaactgccga aaaaaacgtt 600
cttatgtttc ccggaccttg ggggatcaat aatccaatag cntactcttc ncgcc 655

<210> 132
<211> 566
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(566)
<223> n = A,T,C or G

<400> 132
agggtnncac aaagcgctat gttacttagc tgtacgtgtc gtcattntca tgtggtggat 60
tcgagcatca cagctctacg tgtgtcagct ctcacgtctg caccagacgc tgaagcaaga 120
gtacagtgca agtctccaca agcctcccag ccccatcgag aaacatctcc aaagccaaag 180
ggcgcccnaa aaccacngtg tacacctgcc ccatcccggg agaaatgacc agaacaagtc 240
gctgacctgc tggtcaagct ctatccagca ctccctggaa tgggaaacat ggcanccgaa 300
acactacana cacnctcccg tgctggatcg acgtctctcc tctatgcanc tcacgtggac 360
aaacagttgc acagggaact ctctctgtcg tgatgctgan ggtctgccaa cactacccaa 420
aaanctctcc tgttcccggt tataatgcga aggcggcanc cccnctcccg gntctcgcgg 480
tccacaagat gntgcacntn cccgtctatt cttccagcac ccanctggaa ataagcnccn 540
ccatgncctg ggccctgaaa aaaaaa 566

<210> 133
<211> 816
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(816)
<223> n = A,T,C or G

<400> 133
agctngggct nagcgtataa aacttaagct tgggtnaccg agctcgggat ccactcagtc 60
cagtngtggg tgggnaattc ctngnagcca ccctnacagc cagtaagnag atatngtagg 120
gtaaattgtt aagggnaagt cagcacttac attaaagtaa aattgggctc acaaaccccg 180
nacacagtna gcattttgtn gccaatttct gggttgggaa tgggtgaaca aacattgctg 240
ggaagccaag tngctnaaca ttgccttggg ttcaaggggg natgggnaaa gtcacccgtt 300
aaggggatgg gcaattgcca gtgggaaacc caccgcttgc ttgaaggctc tgggacttgc 360
atccttacca cccaaactcc gtccaacttg gacaaagccc ttggccgcct tgcctctcca 420
ggaatgtctt acaaaaattg ggtgggttat tgggttactg gttccttgtt gggcccgaan 480
ttgggaaaaa cttgggttgt tctcaaaacc cgggttattg ggttgggtca ccttttggct 540
cccagnttca aacgtttaca aacggggaaa gtnaaaaatc ttgttcgaaa aattgccacc 600
cattgnaaaa gcttttggaa nttggaaaac tcttccttgg gggggacaaa ttgtttgggg 660
gctttccaat tgntcaaaaa aattgttgtt cttgttcaaa agggatgttt nccgttccgt 720
ggggccaaac cgttttgctt gggttgaaca gccaaaaaaa tttgnaancc ccacccaant 780
tggggaaagc caagcnttgg ggtttcactg gcttcc 816

<210> 134
<211> 451
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(451)
<223> n = A,T,C or G

<400> 134
tttgnangag agggtcacct gggcagccct gacttttgtc ccctggcaaa gggaccttca 60
gtgaccttgg ccctaggaga gcctctgagc acgtcagcca tgtcgaaccg ctcaggaagg 120
gcagcaagaa tttggcttct gacctctgcc tctcctactc gccatctgca ctgggtgtgg 180
ttgtgcccat tttacagatg aggaggctgg ggcatcgacc agctgaatgc cttgtcccag 240
gtactgcgta agcagagctg gcagttgaac cccgtgtcct ggttgtcgct gggggtgggc 300
tgcaccctga cttgtgaggc cagnagcaag gnttgcacgt gacttcgtga ccgtcaccca 360
gctctgcagc acatcccgtg acccanctca tccaggccgn atgcaaacct gttgccaggc 420
ganaaaacca agtcaccgca canctgtggg t 451

<210> 135
<211> 658
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(658)
<223> n = A,T,C or G

<400> 135
gtggtatctg ccttcccagg aggcaggagt ggggccccca actgatgagc tcatggtgca 60
ctcttagctt ttaagacttg tcatacaggg tgcaataaaa caaaatgtgc cactcaaaat 120
gtacttttt ggtatatttt gatcttgctg ttaagagggg ctacaattca gagaggctgc 180
agacacagaa atagccctga aaagctttct tctctggcag agatttgcaa gtgctgagga 240
aatacacgtt agtgaagtga acagaggaga aaagcatttc tctgaggcac accccacccc 300
caccttatct gcctaattgg atcaaggaaa gattaactcc caggaaaaac agactgagat 360
cctaatgctt taaaggtctg actgagaaac ttctccatag gccactgtct atcttcctga 420
gggcancttg ggggagcccc tgagagactc acatcttgtg tggggacagc cttggctcac 480
caagcatacc tctctctctt ccccattacc tgaaacccac ctcccnaaaa ccccagcccc 540
tattctctct gtagcctcag gatgtgaaga aatcttcatc attgggcctc ttggagctca 600
tatttgctgc tcntgtnntg tatatnaatt attgcattta tggtaatatt cctttgcc 658

<210> 136
<211> 478
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(478)
<223> n = A,T,C or G

<400> 136
gaagtctcgc gagtataaga acagtaacca gctccgggag taccagctgg aagggatgaa 60
ctggcttctt tttaactggt ataacagaaa aaactgtatt ttggctgatg agatgggcct 120
agggaaaacc atccagtcca tcacattcct ttcagaaata tttctgagag gaatccacgg 180
ccctttctc attatcgccc ctctctccac catcactaac tgggagcggg agttccggac 240
atggacagag atgaatgcca ttgtgtacca cggcagccag atcagcaggc agatgatcca 300

gcagtatgaa atggtgtaca gagacgccca gggaacccct ttcaggagtc ttcaagttcc 360
acgtcgtcat cacaacnttt gaatgatcct agcagactgc ccagagttga agaagaattc 420
actggaactg tgtggataat tggatgaaac cccccagact ggaagaatan ggaactgc 478

<210> 137
<211> 612
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(612)
<223> n = A,T,C or G

<400> 137
gcaggggctc ttgcaaatta acacaaaata ataattaaaa atgaaacgaa attgaggata 60
ttcttagaaa gggtgaagga catgaaatac attactatct gggatttcaa cctttccaaa 120
ggtcaataaa tccccaaata aaatgtaaat ccaaggctac ctgagaattc catttctgtt 180
gcatctttgt tcatgatgag catatgtctt ttcattttga ggacttttta aaagagaaga 240
gtgacacaca atgcaacatg gacaaggaat gaaaattgct ttagacactg cactttgaac 300
atacaaacct gggaggtgcc agggtctgac actgtatatt tcttcctttg atctgattct 360
tccaaacagg atccatgtac tggcaaattt ccctagtgtt ccctggtaag catcaaagta 420
aaccactggt tggcctcggt atttctacat tggctttctc cattgntttt atacataaaa 480
aaaanaaaaa gaaagaaaac tcactgggca ttttacatgg ggtttccata ttggtcctta 540
atcattcagt ttgaaagtaa atcaaagagg aatgaanagt taaagngctt tgaaattggg 600
gtgaaaactt ca 612

<210> 138
<211> 478
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(478)
<223> n = A,T,C or G

<400> 138
gcaggggctc ttgcaaatta acacaaaata ataattaaaa atgaaacgaa attgaggata 60
ttcttagaaa gggtgaagga catgaaatac attactatct gggatttcaa cctttccaaa 120
ggtcaataaa tccccaaata aaatgtaaat ccaaggctac ctgagaattc catttctgtt 180
gcatctttgt tcatgatgag catatgtctt ttcattttga ggacttttta aaagagaaga 240
gtgacacaca atgcaacatg gacaaggaat gaaaattgct ttagacactg cactttgaac 300
atacaaacct gggaggtgcc agggtctgac actgtatatt tcttcctttg atctgattct 360
tccaaacagg atccatgtac tggcaaattt ccctagtgtt ccctggtaag catcaaagta 420
aaccactggn tggcctcggt atttctacat tggctttctc cattggtttt atacataa 478

<210> 139
<211> 597
<212> DNA
<213> Homo sapien

<400> 139
gttatttggt agttttagag atgaggaact aaggacccag ttgctcagtg tttcctagct 60
agtgaataga gactagacac caagtgttct acgtgcagac tttatactgc tcagcctggc 120
acacaaaatg gcaatggcat agtccccaga ctgtggtccc aactgtctct ttcctaacag 180
ctccccaggc acccacactt ttctgcctct ttttcaatct gtacccttga ccctcctcct 240
ttttctgctt tgtcagactc cttaaggcac ttcataaatt aaccatttcc agggatttcc 300
cctcacacat gagttattcc agtggacagg gcagcctcat gggtgcctgt ggagggtgaa 360

gggtctgcct ggccgtaggt gtgatcacac actcccgttg taacccctgc ctcctgtgac 420
acttgctgcc ccacgattta gctgctttgt gttccgtgcc tcctgtttgc tggtgaactc 480
ctgagttggg gggcgtcatt ccctccactg tagttcttcc gcgatgctga atccacccac 540
ggtcagcacc actcggaaat acttcacagt cctgtagagg aagacaggtc caggttt 597

<210> 140
<211> 368
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(368)
<223> n = A,T,C or G

<400> 140
tttacatcta gactccacag acagaaacgt ttcattttta ttgagttaat tttgaaatat 60
atgaatccct gacccattgt tatcactagc tgttactcta tcaggacagt tgctgaagtt 120
ttttgtcact aaatttaaaa atcaactatc aggttgtccc ttggatgacc tgagatttct 180
agagacaaaa gaaatctatt cttcctgatt gaagaaagag tctgagattt tttttaaacc 240
actgatttgg ggatcagggt gtagccagtg tctcaaactc tcccctgtcc ctttttgtt 300
ttgctcaagg agtgggctnt gaggnctcaa gaattggggt ngttactggt ttatttttga 360
ttaggggg 368

<210> 141
<211> 674
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(674)
<223> n = A,T,C or G

<400> 141
aatgtcaatc tttgctcggt cagtgaggat gtcgcctgtt gagggaaaaa tagtagctgt 60
tgccatattc ctttaactcc ccccccccgc cccccgcaat atgtcccctg aataaacttt 120
gtgggtagtt tttcttcatt cccagaactg ttatgaggta agttcagaaa ttgccagctt 180
cctgatgctc tatgctttga acacacaaaa taatcaaagg tgctctttag taggatcctt 240
tccctatcaa aataacagta acacccaatc tgaggcctca agcccactcc ttgagcaaaa 300
caaaaaaggg acaggggaga gtttgagaca ctggctacac cctgatcccc aaatcagtgg 360
tttaaaaaaa atctcagact ctttcttcaa tcaggaagaa tagatttctt ttgtctctag 420
aaatctcagg tcatccaagg gacaacctga tagttgattt ttaaatttag tgacaaaaaa 480
actttcagca actgtcctga taggagtaac caggctagnt ggataaccaa atggggtnca 540
agggggaatn tcataatatt ttcaaaaaat taaaccttca attaaaaaaa tggaaaaacc 600
ggttttcntg gtcctggtgg ggaggttctt aagnatggta aaaaaaggaa atttccccac 660
ccaacnacct tggg 674

<210> 142
<211> 669
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(669)
<223> n = A,T,C or G

<400> 142

gttggaaact tantcctcaa tgcaatagtg ttgagatgtg ggacctttaa gtgataatta 60
gatcatgagg gatttgcctc attcattaat tattgctatt atctcaggtg agttagttat 120
cggagattga aatcctgata aaaagttgag tttgttctct ctgtctctct ctctctctcc 180
actctagaat tgtaaaaaac taatctctat tctgcataaa ttacccagtc tcaggtattc 240
cattatatta gcaggaaatg gactaagaca ctactttata aaattttgca gtttccaatg 300
ttcagctttt ccttgatccg gcttcatcta catttttctt tgcttgttac tgatggtgaa 360
attttcctgt tgtctttcat ttatggctta cactatcaca tgctctctat taattcatgc 420
cttctatttc cttctgttgt ttttggaagc atctcttttc atgggctcat tttagctctg 480
taagacatat cgaaaactca cttgattcct cctgcatgca tagagctctg ctggggaagt 540
ctccttctgc atgctacgcc ttcccaccaa agacaaggct ttgcttattt gcncattctg 600
tttaacgtct gccaaatatg nggtcttgac ncataagaaa actggtttga nccgcaaaan 660
aaaattttg 669

<210> 143
<211> 501
<212> DNA
<213> Homo sapien

<400> 143
agaccttatt tggtaatctg ctgtcttcca gtgtctctgc attagatacc attactacag 60
tagcacttgg atctctcaca tctattccag aaaatgtgtc tactcatgtt tctcagattt 120
ttaatatgat actaaaagaa caatcattag cagcagaaag taaaactgta ctacaggaat 180
tgattaatgt actcaagact gatcttctaa gttcactgga aatgatttta tccccaactg 240
tggtgtctat actgaaaatc aatagtcaac taaagcatat tttcaagact tcattgacag 300
tggccgataa gatagaagat caaaaaaagg aactagatgg ctttctcagt atactgtgta 360
acaatctaca tgaactacaa gaaaatccat ttgttccttg gttgagtcac aaaagcaatg 420
tggaaaccta actgaagacc tgaagacaat aaagcagacc cattcccagg aactttgcaa 480
gttaatgaat ctttggacag a 501

<210> 144
<211> 501
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(501)
<223> n = A,T,C or G

<400> 144
gatatctcag cacctgactt acacatctta catcctcaag caaactcccc agggcacatt 60
tttagttggc cagccatcac cccagacttc tggaaaacaa ctcaccactg ggtcagtggt 120
ccaaggaaca ctgggagtca gcacatcttc tgcacaagga caacaaacgc taaaagtcat 180
ctctggacag aaaaccacat tgtttacaca ggcagcccat ggaggacagg catctctaat 240
gaaaatatcc gatagcacgt tgaagactgt gccagccacc tcacagctct cgaagcctgg 300
aaccacaatg ctgagagtag caggaggggt tatcacaact gccacttccc ctgccgtggc 360
cctctcagca aacggtcctt gccaacagtc tgaaggaatg gctnccgtgt cttcatctac 420
ggncaagttc tgtaacgaaa acttctgggc agcaacaaag tgtgtgtgan ccaagccacc 480
cgtggggaac cttgcaaggn t 501

<210> 145
<211> 501
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(501)
<223> n = A,T,C or G

<400> 145
ggaatccgag ccggctaccc cctctccgag cgccagcagg tggcccttct catgcagatg 60
acggccgagg agtctgccaa gagcccagtg gacacaacac caaagcaccc ctcccagtct 120
acagtgtgtc agaagggaac gcccaactct gcctcaaaaa ccaaagataa agtgaacaag 180
agaaacgagc gtggagagac ccgcctgcac cgagccgcca tccgcgggga cgcccggcgc 240
atcaaagagc tcatcagcga gggggcagac gtcaacgtca aggacttcgc aggctggacg 300
gcgctgcacg aggcctgtaa ccggggctac tacgacgtcg cgaagcaact gctggctgca 360
ggtgcggagg tgaacaccaa gggcctagat gacgacacgc cttttgcacg acgcttgcca 420
acaacgggca ctacaaggtg gtgaaactgc ttgttgcggt acnganggaa cccgnacaaa 480
acaacaggaa aagcgaagac c 501

<210> 146
<211> 501
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(501)
<223> n = A,T,C or G

<400> 146
ggcccggaca cggacaggat tgacagattg atagctcttt ctcgattccg tgggtggtgg 60
tgcatggccg ttcttagttg gtggagcgat ttgtctggtt aattccgata acgaacgaga 120
ctctggcatg ctaactagtt acgcgacccc cgagcggtcg gcgtccccca acttcttaga 180
gggacaagtg gcgttcagcc acccgagatt gagcaataac aggtctgtga tgcccttaga 240
tgtccggggc tgcacggccg ctacactgac tggctcagcg tgtgcctacc ctacgccggc 300
aggcgcgggt aacccgttga accccattcg tgatggggat cggggattgc aattattccc 360
catgaacgan gaattcccag taagtgcggg tcataagctt attccgcact tacctgggga 420
gaagcctttt ggtcttccgg ggacnaaaac agctttgttg ctgaacgcng gcagcaccgg 480
tcgcgccgtc cggtggttac c 501

<210> 147
<211> 501
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(501)
<223> n = A,T,C or G

<400> 147
cagcgccgcc gcccggcccc tccagcttcc cggaccatgg ccaacctgga gcgcaccttc 60
atcgccatca agccggacgg cgtgcagcgc ggcctggtgg gcgagatcat caagcgcttc 120
gagcagaagg gattccgcct cgtggccatg aagttcctcc gggcctctga agaacacctg 180
aagcagcact acattgacct gaaagaccga ccattcttcc ctgggctggt gaagtacatg 240
aactcagggc cggttgnggc catggtctgg gaggggctga acgtggtgaa gacaggccga 300
gtgatgcttg gggagaccaa tccagcagat tcaaagccag gcaccattcg tggggacttc 360
tgcattcagg ttggcaggaa catcattcat ggcagtgatt cagtaaaaag tgctgaaaaa 420
gaaatcagcc tatggtttaa gcctgaagaa ctggttgact acaagtcttt ggctcatgac 480
tgggtctatn aataagaagg g 501

<210> 148
<211> 501
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(501)
<223> n = A,T,C or G

<400> 148
actcttagct tgtcggggac ggtaaccggg acccggtgtc tgctcctgtc gccttcgcct 60
cctaatccct agccactatg cgtgagtgca tctccatcca cgttggccag gctggtgtcc 120
agattggcaa tgcctgctgg gagctctact gcctggaaca cggcatccag cccgatggcc 180
agatgccaag tgacaagacc attgggggag gagatgactc cttcaacacc ttcttcagtg 240
agacgggcgc tggcaagcac gtgccccggg ctgtgtttgt agacttggaa cccacagtca 300
ttgatgaagt tcgcactggc acctaccgcc agctcttcca ccctgagcag ctcatcacag 360
gcaaggaaga tgctgccaat aactatgccc gagggcacta caccattggc aaggagatca 420
ttgaccttgt gttggaccga attcgcaagc tggctgacag tgcaccggtc ttcagggctt 480
cttggttttn cacagctttg g 501

<210> 149
<211> 501
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(501)
<223> n = A,T,C or G

<400> 149
cgcccgggca ggaatagaag atgaacaaac ccataacacc atcaacatat gtgcgctgcc 60
tcaatgttgg actaattagg aagctgtcag attttattga tcctcaagaa ggatggaaga 120
agttagctgt agctattaaa aaaccatctg gtgatgatag atacaatcaa gtttcacata 180
aggagatttg aagcattctt caaactggaa aaagtcccac ttcttgaata ctgtttgact 240
gggggcacca caaattggac agttggtgat cttgtggatc ttttgatcca aaatgaattt 300
ttgctcctgc gagtcttttg ctcccagatg ctgttcccaa actgctaata cactaccttc 360
taaagaagct ataacagttc agcaaaaaca gatgcctttc tgtgacaaag acaggacatt 420
gatgacacct gtgcanaatc ttgaacaaag ctatatgcca cctgactcct caagtccana 480
aaataaaagt ttaaaagtta g 501

<210> 150
<211> 501
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(501)
<223> n = A,T,C or G

<400> 150
cagcacagga tactgatatt ctgtcagctg aaaagcatgc ttgatatagt agagcatgat 60
ctcctcaaac ctcacttgcc ctctgtcact tatttgagat tagatggcag catacctcct 120
ggtcagaggc attccattgt ttcccggttt aataatgatc catctataga cgttctgtta 180
cttaccactc acgttggtgg cctgggactt aatttgacag gcgctgacac agtagtattt 240
gtggagcatg actggaantc tatgcgagat ctacaagcca tggaccgggc ccatcgcatt 300
gggcagaaac gtgtggttaa cgtatccgat tgataaccag aggaacattg gaagaaaaaa 360
taatggggtt gcagaaaatt caagatgaac catagcgaat ctgttattag ccaagagaat 420
tcttagtttg canacatggg ggactgatca gctttcttga atctgtttac tcttggataa 480
gggatggcaa aagcagaaaa a 501

<210> 151

<211> 501
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(501)
<223> n = A,T,C or G

<400> 151
atggaggggt gtgtgtctaa cctaatggtc tgcaacctgg cctacagccg gaagctggaa 60
gagttgaagg agagtattct ggccgataaa tncctgnnta ctacaactga ccaggacagc 120
agaactgcat tgcactgggc atgctcagct ggacatacag aaattgttga atttttgttg 180
caacttggag tgccagtgaa tgataaagac gatgcaggtt ggtctcctct tcatattgcg 240
gcttctgctg gccgggatga gattgtaaaa gcccttctgg gaaaaggtgc tcaagtgaat 300
gctgtcaatc aaaatggctg tactccctta cattatgcag cttcgaaaaa caggcatgag 360
atcgctgtca tgttactgga aggcggggct aatccagatg ctaaggacca ttatgaggct 420
acagcaatgc accgggcagc agccaagggt aacttgaaga tgattcatat ccttctgtac 480
tacaaagcat ccacaaacat c 501

<210> 152
<211> 501
<212> DNA
<213> Homo sapien

<400> 152
gcccgccgaa gccgcgccag aactgtactc tccgagaggt cgttttcccg tccccgagag 60
caagtttatt tacaaatgtt ggagtaataa agaaggcaga acaaaatgag ctgggctttg 120
gaagaatgga aagaaggact gcctacaaga gctcttcaga aaattcaaga gcttgaagga 180
cagcttgaca aactgaagaa ggaaaagcag caaaggcagt ttcagcttga cagtctcgag 240
gctgcgctgc agaagcaaaa acagaaggtt gaaaatgaaa aaaccgaggg tacaaacctg 300
aaaagggaga atcaaagatt gatggaaata tgtgaaagtc tggagaaaac taagcagaag 360
atttctcatg aacttcaagt caaggagtca caagtgaatt tccaggaagg acaactgaat 420
tcaggcaaaa aacaaataga aaaactggaa caggaactta aaagtgtaaa tctgacttga 480
aagaagcaac aactggcatc t 501

<210> 153
<211> 501
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(501)
<223> n = A,T,C or G

<400> 153
agagagagag agagagagag gagcgagaga gtgtgagcga gaaagaataa aaggaaagaa 60
gattttctct atgtatataa agatggccac gttagcaaac ggacaggctg acaacgcaag 120
cctcagtacc aacgggctcg gcagcagccc gggcagtgcc gggcacatga acggattaag 180
ccacagcccg gggaacccgt cgaccattcc catgaaggac cacgatgcca tcaagctgtt 240
cattgggcag atcccccgca cctggatgag aaggacctca agcccctctt cgaggagttt 300
ggcaaaatct acgagcttac ggttctgaag gacaggttca caggcatgca caaaggctgc 360
gccttcctca cctactgcga gcgtgagtca gcgctgaagg cccagagcgc gctgcacgag 420
cagaagactc tgcccgggat gaacccggcc cgatccnagg tgaagccttg cggacagcga 480
gaaccgagga gatagaaact c 501

<210> 154
<211> 501

<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(501)
<223> n = A,T,C or G

<400> 154
ttccttcctg tgtgaggccg gctgagggca cttgctcttg ctgtttctgc ccctgggtta 60
acattcaaga tggtacatgc tgaagccttt tctcgtcctt tgagtcggaa tgaagttgtt 120
ggtttaattt tccgtttgac aatatttggt gcagtgacat actttactat caaatggatg 180
gtagatgcaa ttgatccaac cagaaagcaa aaagtagaag ctcagaaaca ggcagaaaaa 240
ctaatgaagc aaattgggag tgaaaaatgt gaagctctca gaatatgaaa tgagtattgc 300
tgctcatctt gtagaccctc ttaatatgca tgttacttgg agtgatatag caggtttaga 360
tgatgtcatt acggatctga aagacacagt catcttacct atcaaaaaga aacatttgtt 420
tgagaattcc aggcttctgc agcctccaaa aggtgntctt ctctatgggc ctccagctgt 480
ggtaaaacgt tgattgccaa g 501

<210> 155
<211> 601
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(601)
<223> n = A,T,C or G

<400> 155
aggaggagga acagcaggag gaggaactca aagtactgct ggccctggag ggatatctca 60
gcacctgact tacacatctt acatcctcaa gcaaactccc cagggcacat ttttagttgg 120
ccagccatca ccccagactt ctggaaaaca actcaccact gggtcagtgg tccaaggaac 180
actgggagtc agcacatctt ctgcacaagg acaacaaacg ctaaaagtca tctctggaca 240
gaaaaccaca ttgtttacac aggcagccca tggaggacag gcatctctaa tgaaaatatc 300
cgatagcacc ttgaagactg tgccagccac ctcacagctc tcgaagcctg gaaccacaat 360
gctgagagta gcaggagggg ttatcacaac tgccacttcc cctgccgtgg ccctctcagc 420
aaacggtcct gcacaacagt ctgaaggaat ggctcccgtg tcttcatcta cggtcagttc 480
tgtaacgaaa acttctgggc agcagcaagt gtgtgtgagc caggccaccg tgggaacctg 540
caaggntgcc accccccgt cgtcagcgcc acgtncctcg tgctacacca aaccccatct 600
c 601

<210> 156
<211> 501
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(501)
<223> n = A,T,C or G

<400> 156
caagaaagga gaaagagagc tcaaaatcgg agacagagta ttggttggtg gcactaaggc 60
tggtgtagtc cggtttcttg gggagaccga ctttgccaag ggggagtggt gtggcgtgga 120
gttagatgag ccacttggga agaatgatgg cgctgttgct ggaacaaggt attttcagtg 180
tcaacccaaa tatggcttgt tcgctcctgt ccacaaagtt accaagattg gcttcccttc 240
cactacacca gccaaagcca aggccaacgc agtgaggcga gtgatggcga ccacgtccgc 300
cagcctgaag cgcagccctt ctgcctcttc cctcagctcc atgagctcag tggcctcctc 360

tgtgagcagc angcccagtc ggacaggact attgactgaa acctcctccc gttacgccag 420
gaagatctcc ggtaccactg ccctccanga ggcccttgaa ggaaaaacan cagcacattg 480
agcancttgc tggcnggaac c 501

<210> 157
<211> 501
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(501)
<223> n = A,T,C or G

<400> 157
caccctcttc gtcgcttcgg ccagtgtgtc gggctgggcc ctgacaagcc acctgaggag 60
aggctcggag ccgggcccgg accccggcga ttgccgcccg cttctctcta gtctcacgag 120
gggtttcccg cctcgcaccc ccacctctgg acttgccttt ccttctcttc tccgcgtgtg 180
gagggagcca gcgcttangc cggagcgagc ctgggggccg cccgccgtga agacatcgcg 240
gggaccgatt caccatgnag ggcgccggcg gngcgaacga caagaaaaag ataagttctg 300
aacgtcgaaa agaaaagtct cgagatgcag ccanatctcg gcgaagtaaa gaatctgaag 360
ttttttatga gcttgctcat cagttgccac ttccacataa tgtgagttcg catcttgata 420
angcctcttg tgatgaggct taccatcagc tatttgcgtg tgaggaaact tctggatgct 480
ggtgatttgg atattgaaga t 501

<210> 158
<211> 501
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(501)
<223> n = A,T,C or G

<400> 158
acggggtcac ccacacggtg cccatctacg agggctacgc cctcccccac gccatcctgc 60
gtctggacct ggctggccgg gacctgaccg actacctcat gaagatcctc actgagcgag 120
gctacagctt caccaccacg gccgagcggg aaatcgtgcg cgacatcaag gagaagctgt 180
gctacgtcgc cctggacttc gagcaggaga tggccaccgc cgcatcctcc tcttctctgg 240
agaagagcta cgagctgccc gatggccagg tcatcaccat tggcaatgag cggttccggt 300
gtccggaggc gctgttccag ccttccttcc tgggtatgga atcttgcggn attcacgana 360
ccaccttcaa ctccatcatg aagtgtgacg tggacatccg caaagacctg tacgccaaca 420
ccgtgctgtc gggcggnacc accatgtacc cgggcattgc cgacaggatg caaaaaggag 480
atcacccgcc cttggcgccc a 501

<210> 159
<211> 501
<212> DNA
<213> Homo sapien

<400> 159
cgagcgggac tggctgggtc ggctgggctg ctggtgcgag gagccgcggg gctgtgctcg 60
gcggccaagg ggacagcgcg tgggtggccg aggatgctgc ggggcggtag ctccggcgcc 120
cctagctggt gactgctgcg ccgtgcctca cacagcccga ggcgggctcg gcgcacagtc 180
gctgctccgc gcgcgcgccc ggcggcgctc caggtgctga cagcgcgaga gagcgcggcc 240
ctcaggagca aggcgaatgt atgacaacat gtccacaatg gtgtacataa aggaagacaa 300
gttggagaag cttacacagg atgaaattat ttctaagaca aagcaagtaa ttcaggggct 360
ggaagctttg aagaatgagc acaattccat tttacaaagt ttgctggaga cactgaagtg 420

tttgaagaaa gatgatgaaa gtaatttggt ggaggagaaa tcaaacatga tccggaagtc 480
actggagatg ttggagctcg g 501

<210> 160
<211> 487
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(487)
<223> n = A,T,C or G

<400> 160
aagatctcag tctgactctt ttggaacaag tcaaactgcc catgatgttg ctgatcagcc 60
aaggcctgga tcagagggga gcttctgtgc atcttcaaac tctccaatgc actcccaagg 120
ccagcagttc tctggtgtct cccaacttcc tggacctgtg ccacttcagg agtaactgat 180
acacagaata ctgtaaatat ggcccaagca gatacagaga aattgagaca gcggcagaag 240
ttacgtgaaa tcattctcca gcagcaacag cagaagaaga ttgcaggtcg acaggagaag 300
gggtcacagg actcacccgc agtgccttca tccanggcct ctttaacact ggcaaccaag 360
agaatggtta acccaggctt ttaaccaana acccccacct tccttttcct gggggaacat 420
ttaggtcttc ctggttggcc ccttcctttt anggaacctt anaatttgct tggtttttcc 480
ccnaaaa 487

<210> 161
<211> 501
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(501)
<223> n = A,T,C or G

<400> 161
ggttcccggc ccagtcccgt cctgcagcag tctgcctcct ctttcaacat gacagatgcc 60
gctgtgtcct tcgccaagga cttcctggca ggtggagtgg ccgcagccat ctccaagacg 120
gcggtagcgc ccatcgagcg ggtcaagctg ctgctgcagg tgcagcatgc cagcaagcag 180
atcactgcag ataagcaata caaaggcatt atagactgcg tggtccgtat tcccaaggag 240
cagggagttc tgtccttctg gcgcggtaac ctggccaatg tcatcagata cttccccacc 300
caggctctta acttcgcctt caaagataaa tacaagcaga tcttcctggg tggtgtggac 360
aagagaaccc agttttggcg ctactttgca gggaatctgg catcgggtgg tgccgcangg 420
gccacatccc tgtgttttgt gtaccctctt gattttgccc gtacccgtct ancanctgat 480
gtggggtaaa agctggagct g 501

<210> 162
<211> 501
<212> DNA
<213> Homo sapien

<400> 162
gaaaaagaaa aagaactaca acggcagaaa gaaaaggaaa aagaactaca aaagatgaaa 60
gaacaagaaa aggaatgtga gctggagaag gaaagggaaa aattagagga gaaaattgaa 120
cccagagaac ctaatttaga gcccatggta gaaaaacaag aaagtgaaaa cagctgtaat 180
aaagaggagg aacccgtttt cactagacaa gacagcaatc gcagtgaaaa ggaagccaca 240
ccagtggtgc atgaaacaga accagaatca gggtctcaac ctcggccggc tgtattatct 300
ggctatttca aacagtttca gaagtcttta cctccacgat tccagcggca gcaggaacag 360
atgaaacagc agcagtggca gcagcagcaa cagcaaggtg tacttccaga ctgttccttc 420
caaccgtcca gtagtactgt ccctcctccc cacacagacc tcttttcagc ctatgcagcc 480

tctcctcagc atttggcttc t 501

<210> 163
<211> 501
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(501)
<223> n = A,T,C or G

<400> 163
gagctcgacc agttgcctga cgagagctct tcagcaaaag cccttgtcag tttaaaagaa 60
ggaagcttat ctaacacgtg gaatgaaaag tacagttctt tacagaaaac acctgtttgg 120
aaaggcagga atacaagctc tgctgtggaa atgccttttc agaaattcaa aacgaagtcg 180
actttttttct gatgaagatg ataggcaaat aaatacaagg tcacctaaaa gaaaccagag 240
ggttgcaatg gttccacaga aatttacagc aacaatgtca acaccagata agaaagcttc 300
acagaagatt ggttttcgat tacgtaatct gctcaagctt cctaaagcac ataaatggtg 360
tatatacgag tggttctatt caaatataga taaaccactt tttgaaggtg ataatgactt 420
ttgtgtatgt ctaaaggaat cttttctaat ttgaaaacaa gaaagttaac aagagtagaa 480
tggggaaaaa ttcngcggct t 501

<210> 164
<211> 501
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(501)
<223> n = A,T,C or G

<400> 164
cgggtgcgcg cccacgaccg ccagactcga gcagtctctg gaacacgctg cggggctccc 60
gggcctgagc caggtctgtt ctccacgcag gtgttccgcg cgccccgttc agccatgtcg 120
tccggcatcc atgtagcgct ggtgactgga ggcaacaagg ggcatcggct tggccatcgt 180
gcgcgacctg tgccggctgt tctcggggga cgtggtgctc acggcgcggg acgtgacgcg 240
gggccaggcg gccgtacagc agctgcaggc ggagggcctg agcccgcgct tccaccagct 300
ggacatcgac gatctgcaga gcatccgcgc cctgcgcgac ttcctgcgca aggagtacgg 360
gggcctggac gtgctggtca acaacgcggg catcgccttc aaggttgctg atcccacacc 420
ctttcatatt caagctgaag tgacgatgaa aacaaatttc tttggtaccc ganatgtgtg 480
cacagaatta ctccctctaa t 501

<210> 165
<211> 501
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(501)
<223> n = A,T,C or G

<400> 165
ccggtgaagg accgcgaggc cttccagagg ctcaacttcc tgtaccaggt gagtctgcga 60
caagggcccc acggggacgg tgctcggcgt cccagagtga ctgctcccct cccgcaggcc 120
gcccattgtg tccttgccca ggacccccgag aaccangcgc tggcgaggtt ttactgctac 180
actgagagga ccattgcgaa gcggctcgtc ttgcggcggg atccctcggt gaagaggact 240

ctctgtcgag gctgctcttc cctcctcgtc ccgggcctca cctgcaccca ccgccagaga 300
cgctgcaggg gacagcgctg gaccgtacag acctgcctaa catgccagcg cagccaacgc 360
tnnctcaatg atcccnggca tttactntgg ggagacnggn ctgaggccca actcgggagc 420
caagcagatt ccaaaccact acaacccttg ccaaacacag cccactccat ttcagaccgc 480
cttcctgagg agaaaatgca g 501

<210> 166
<211> 412
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(412)
<223> n = A,T,C or G

<400> 166
atgtccaagc cggtggacca cgtcaagcgg cccatgaacg ccttcatggt gtggtcgcgg 60
gctcagcggc gcaagatggc ccaggagaac cccaagatgc acaactcgga gatcagcaag 120
cgcttgggcg ccgagtggaa actgctcaca gagtcggaga agcggccgtt catcgacgag 180
gccaagcgtc tacgcgccat gcacatgaag gagcaccccg actacaagta ccggccgcgg 240
cgcaagccca agacgctgct caagaaggac aagttcgcct tcccggtgcc ctacggcctg 300
ggcggcgtgg cggacgccga gcaccctgcg ctcaaggcgg gcgccgggct gcacgcgggg 360
gcgggcggcg gnctggtgcc tgagtcgctg ctcgccaatc ccgagaaggc gg 412

<210> 167
<211> 501
<212> DNA
<213> Homo sapien

<400> 167
aaatgcaagt tgatctggag aaagaattac aatctgcttt taatgagata acaaaactca 60
cctcccttat agatggcaaa gttccaaaag atttgctctg taatttggaa ttggaaggaa 120
agattactga tcttcagaaa gaactaaata aagaaagttg aagaaaaatg aagctttgcg 180
ggaagaagtc attttgcttt cagaattgaa atctttacct tctgaagtag aaaggctgag 240
gaaagagata caagacaaat ctgaagagct ccatataata acatcagaaa aagataaatt 300
gttttctgaa gtagttcata aggagagtag agttcaaggt ttacttgaag aaattgggaa 360
aacaaaagat gacctagcaa ctacacagtc gaattataaa agcactgatc aagaattcca 420
aaatttcaaa acccttcata tggactttga gcaaaagtat aagatggtcc ttgaggagaa 480
tgagagaatg aatcaggaaa t 501

<210> 168
<211> 501
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(501)
<223> n = A,T,C or G

<400> 168
ggggcccgcg gagctcgcgc caggctcctg ggaaaggacg gggagtgtta ccggggagca 60
gctgctccat tgtgcctcga ggccccgatc gggctaggcc gacggcctcc ctcccttcac 120
ctttcctctc ctggcggggt tcggcggcgg gcgagtgact tgcggccacg cctgaaaggc 180
gactctcctg attcaagatg accaacgaag aacctcttcc caagaaggtt cgattgagtg 240
aaacagactt caaagttatg gcaagagatg agttaattct aagatggaaa caatatgaag 300
catatgtaca agctttggag ggcaagtaca cagatcttaa ctctaatgat gtaactggcc 360
taagagagtc tgaagaaaaa ctaaagcaac aacagcagga gtctgcacgc agggaaaaca 420

tccttgtaat gcgactagca accaaggaac aagagatgca agagtgtact acttaaatcc 480
agtacctcaa gcaagtccan c 501

<210> 169
<211> 501
<212> DNA
<213> Homo sapien

<400> 169
gctgtgcggc ggtcccgcgc ccggcgatgt tcccgggcac tccctgagta gcggcagctt 60
atcccccgcc cgctagcccg ccctggtccc cggctcgctc gctggctggc gcggccccgg 120
ccccgctctg cgtcggcccc gccgcggtgg aggcgcgcga gggggacgcg gccggggatg 180
agcggattgc gggtgaactc gccgcccggg ggccccgcga agccgtgagc cgctgctttt 240
ctccgagtcg ccgccctgcc cttggatttg agatcatgtc catccacatc gtggcgctgg 300
ggaacgaggg ggacacattc caccaggaca accggccgtc ggggcttatc cgcacttacc 360
tggggagaag ccctctggtc tccggggacg agagcagctt gttgctgaac gcggccagca 420
cggtcgcgcg tccggtgttc accgagtatc aggccagtgc gtttgggaat gtcaaagctg 480
gtggtccacg actgtcccgt c 501

<210> 170
<211> 501
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(501)
<223> n = A,T,C or G

<400> 170
gcatcctctt gccgttcccg gtgtttgggc cttgcctgtg acggtgggaa aagaaaatgg 60
ccttgctgtg ctacaaccgg ggctgcggtc agcgcttcga tcctgagacc aattccgacg 120
atgcttgcac ataccaccca ggtgttccgg tctttcacga tgcattaaag ggttggtctt 180
gctgtaagag aagaacaact gatttttctg atttcttaag cattgtaggc tgtacaaaag 240
gtagacataa tagtgagaag ccacctgagc cagtcaaacc tgaagtcaag actactgaga 300
agaaggagct atgtgaatta aaacccaaat ttcangaaca catcattcaa gcccctaagc 360
cagtagaagc aataaaaaga ccaagcccag atgaaccaat gacaaatttg gaattaaaaa 420
tatctgcctc cctaaaacaa gcacttgata aacttaaact gtcatcaggg aatgaagaaa 480
atnagaaaga agaagacnat g 501

<210> 171
<211> 601
<212> DNA
<213> Homo sapien

<400> 171
agcgacctat cttgaactcc acagccttga tgacttctac ataggaaagt attttggagg 60
agtgttggag tattttatga ttcaagcctt aaatcagaag acaagtgaaa aaatgaagaa 120
aagaaaaatg agcaactcct ttcatggaat tagaccacct caacttgaac aaccagaaaa 180
aatgcctgtc ttaaaggctg aagcgtcaca ttataactct gacttaaata acttgctgtt 240
ctgctgccag tgtgtggacg tggtatttta caaccccaat ttaaagaaag ttgtagaggc 300
ccacaagatc gttctctgcg ctgtaagcca tgttttcatg ctgcttttca atgtgaagag 360
tcccactgac attcaggatt ccagtatcat ccgaactacc caggatcttt ttgctataaa 420
cagagatact gcatttccag gtgctagcca tgaatcttca ggcaacccac cattacgagt 480
cattgttaaa gacgccctct tctgttcttg tttatcagac atccttcgct tcatttattc 540
aggtgctttt cagtgggaag aattggaaga agatatcagg aagaagttga aagattctgg 600
g 601

<210> 172

<211> 501
<212> DNA
<213> Homo sapien

<400> 172
gaccgtttaa aaaactggta tccagctcac atagaagaca ttgactacga ggaaggaaaa 60
gtactcatcc atttcaagcg ttggaaccat cgttatgatg agtggttctg ctgggacagt 120
ccttatttac gccctttaga gaaaatacag ctgaggaaag agggcttgca tgaagaggat 180
ggatcttctg aatttcaaat aaatgagcag gtccttgctt gctggtctga ttgtcgtttt 240
tacccggcca aagtcactgc tgttaacaag gatggtactt acactgtgaa attttatgat 300
ggagtagttc agactgtcaa acatattcat gtcaaagctt tttccaaaga tcagaatatt 360
gtgggtaatg ctaggcctaa agaaacagat cacaaaagtc tttcatcatc tcctgataaa 420
cgagagaagt ttaaagaaca gagaaaagca acagtgaatg tgaagaaaga caaagaagat 480
aaacccttaa agacagaaaa g 501

<210> 173
<211> 501
<212> DNA
<213> Homo sapien

<400> 173
gcgacctatc ttgaactcca cagccttgat gacttctaca taggaaagta ttttggagga 60
gtgttggagt attttatgat tcaagcctta aatcagaaga caagtgaaaa aatgaagaaa 120
agaaaaatga gcaactcctt tcatggaatt agaccacctc aacttgaaca accagaaaaa 180
atgcctgtct taaaggctga agcgtcacat tataactctg acttaaataa cttgctgttc 240
tgctgccagt gtgtggacgt ggtattttac aaccccaatt taaagaaagt tgtagaggcc 300
cacaagatcg ttctctgcgc tgtaagccat gttttcatgc tgcttttcaa tgtgaagagt 360
cccactgaca ttcaggattc cagtatcatc cgaactaccc aggatctttt tgctataaac 420
agagatactg catttccagg tgctagccat gaatcttcag gcaacccacc attacgagtc 480
attgttaaag acgccctctt c 501

<210> 174
<211> 501
<212> DNA
<213> Homo sapien

<400> 174
ccccgggagg cgggccgtcg ggcgcagccg cgaagatgcc gttggaactg acgcagagcc 60
gagtgcagaa gatctgggtg cccgtggacc acaggccctc gttgcccaga tcctgtgggc 120
caaagctgac caactccccc accgtcatcg tcatggtggg cctccccgcc cggggcaaga 180
cctacatctc caagaagctg actcgctacc tcaactggat tggcgtcccc acaaaagtgt 240
tcaacgtcgg ggagtatcgc cgggaggctg tgaagcagta cagctcctac aacttcttcc 300
gccccgacaa tgaggaagcc atgaaagtcc ggaagcaatg tgccttagct gccttgagag 360
atgtcaaaag ctacctggcg aaagaagggg gacaaattgc ggttttcgat gccaccaata 420
ctactagaga gaggagacac atgatccttc attttgccaa agaaaatgac tttaaggcgt 480
ttttcatcga gtcggtgtgc g 501

<210> 175
<211> 501
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(501)
<223> n = A,T,C or G

<400> 175
ccaacatgac cgaacgaaga agggacgagc tctctgaaga gatcaacaac ttaagagaga 60

aggtcatgaa gcagtcggag gagaacaaca acctgcagag ccaggtgcag aagctcacag 120
aggagaacac cacccttcga gagcaagtgg aacccacccc tgaggatgag gatgatgaca 180
tcgagctccg cggtgctgca gcagctgctg ccccaccccc tccaatagag gaagagtgcc 240
cagaagacct cccagagaag ttcgatggca acccagacat gctggctcct ttcatggccc 300
agtgccagat cttcatggaa aagagcacca gggatttctc agttgatcgt gtccgtgtct 360
gcttcgtgac aagcatgatg accggccgtg ctgccgttgg gcctcagcaa agctggagcg 420
ctccactacc tgatgcacaa ctacccactt tcatgatgga aatgaagcat gtctttgaag 480
accctcanag gcgagaggtt g 501

<210> 176
<211> 378
<212> DNA
<213> Homo sapien

<400> 176
ggcggaagag gtgatttatt atatggttgt tacactcggc cacaaataaa cacagaaata 60
gtccagaatg tcacaggtcc agggcagagg accaacatgg gcattttgtt tatgagcaag 120
gtgggtctca gaggtgatcg gcgatcagag ggcgatgaag ttctagatcc attgagacaa 180
gctctagaca gtagcatgca gtcccacaac ttgtaccagc atccccagcg tctggcattc 240
catgtttctg ctcctgtggc ctccacggtg caacaagcta gcggtttact tggacctctg 300
cctcatcttt cttcttttgc gcttcagcct gcgcattcgc ttcttcctcc acttggctct 360
catggcgcag aggtttcc 378

<210> 177
<211> 501
<212> DNA
<213> Homo sapien

<400> 177
ggcagggagc tggacctgga ggcgccgccg cgacagcagc agccatggag gacgagatgc 60
ccaagactct atacgtcggt aacctttcca gagatgtgac agaagctcta attctgcaac 120
tctttagcca gattggacct tgtaaaaact gcaaaatgat tatggataca gctggaaatg 180
atccctattg ttttgtggag tttcatgagc atcgtcatgc agctgcagca ttagctgcta 240
tgaatggacg gaagataatg ggtaaggaag tcaaagtgaa ttgggcaaca acccctagca 300
gtcaaaagaa agatacaagc aatcatttcc atgtctttgt tggtgatctc agcccagaaa 360
ttacaactga agatataaaa gctgcttttg caccatttgg aagaatatca gatgcccgag 420
tggtaaaaga catggcaaca ggaaagtcta agggatatgg ctttgtctcc tttttcaaca 480
aatgggatgc tgaaaacgcc a 501

<210> 178
<211> 501
<212> DNA
<213> Homo sapien

<400> 178
agccccgggc caggccgcgg ccggggcagg agcgcagggg ctttgttatg cacctaaagc 60
catattggaa gctccagaag aaagagcacc ccccggaagt cagcagggaa acgcagagaa 120
ctcctatgaa ccaccaaaag gctgtaaatg atgaaacatg caaagctagc cacataacat 180
caagtgtctt tccttcagcc tctctcggta aagcatcatc tcgaaagcca tttgggatcc 240
tttctccaaa tgttctgtgc agtatgagtg ggaagagtcc tgtagagagc agcttgaatg 300
ttaaaaccaa aaagaatgca ccatctgcaa cgatccacca gggcgaagaa gaaggaccac 360
ttgatatctg ggctgttgtg aaacctggaa ataccaagga aaaaattgca ttctttgcat 420
cccaccagtg tagtaacagg ataggatcta tgaaaataaa aagttcctgg gatattgatg 480
ggagagctac taagagaagg a 501

<210> 179
<211> 501
<212> DNA
<213> Homo sapien

<400> 179
cgggactagg agcgcggcgg ggccggcggc agagctgtcc ggctgcgcgg tggcccgggg 60
ggcccgggcg gcagggcaag cagcgcggcc tcggcctatg cgaccggtgg cgccggcgcg 120
gcttctgcct ggagaggatt caagatgacc aacgaagaac ctcttcccaa gaaggttcga 180
ttgagtgaaa cagacttcaa agttatggca agagatgagt taattctaag atggaaacaa 240
tatgaagcat atgtacaagc tttggagggc aagtacacag atcttaactc taatgatgta 300
actggcctaa gagagtctga agaaaaacta aagcaacaac agcaggagtc tgcacgcagg 360
gaaaacatcc ttgtaatgcg actagcaacc aaggaacaag agatgcaaga gtgtactact 420
caaatccagt acctcaagca agtccagcag cccgagcgtt gccaactgag atcaacaatg 480
gtagacccag cgatcaactt t 501

<210> 180
<211> 571
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(571)
<223> n = A,T,C or G

<400> 180
gagcgtaccg ggttttctcc atgctgtttc ttactctcct cttttgcacc cctcccattt 60
ccctcgtttt tctttgaaaa tttctccccc ctccagttcg ctgtccggcc ctcacatgtg 120
tganaggggc agtgtgccgt taatggccgt gccgggcacc gggccgctct ggtagtgctg 180
ggacatgtga agtctgctgg gggcggcggg ttccggcacc tcggcgccgg ggagatacat 240
gctgatcatg tcccggaggt ccccggcctg gcagggcgcc ctggagtggg aggaagaggt 300
aaccacaggg gggctggagc tggcctcgga cttgaccacc gaacccatgg agccaanagc 360
catgccaggg gtgccctgct gcgagtagga catgctgtag gtgggcgagc cgttcatgta 420
ggtctgcgag ctggtcatgg agttgtactg cagggcgctc acgtcgtaac ggtgcatggg 480
ctgcatctgc gctgcgccgt gcgcattgag gcccgggtgc tgngggtagc ccaactggtc 540
ctgcatcatg ctgtactgcc gntgctccac c 571

<210> 181
<211> 501
<212> DNA
<213> Homo sapien

<400> 181
tgagaccgcc aagatggtgg tgggcgcgtt ccctatggcg aagctgctat acttgggcat 60
ccggcaggtc agcaagccgc ttgccaaccg tattaaggag gccgcccgcc gaagcgagtt 120
cttcaagacc tatatctgcc tcccgccggc tcaactgtat cactgggtgg agatgcggac 180
caagatgcgc atcatgggct tccggggcac ggtcatcaag ccgctgaacg aggaggcggc 240
agccgagctg ggcgcagagc tgctgggcga agccaccatc ttcatcgtgg gcggcggctg 300
cctagtgctg gagtactggc gccaccaggc gcagcagcgc cacaaggagg aggagcagcg 360
tgctgcctgg aacgcgctgc gggacgaggt gggccacctg gcgctggcgc tggaagcgct 420
gcaggcgcag gtgcaggcgg cgccgccaca gggcgccctg gaggaactgc gcacagaact 480
gcaagaggtg cgcgcccact c 501

<210> 182
<211> 501
<212> DNA
<213> Homo sapien

<400> 182
ccccagcaga catgtttgcc aaggcctttc gggtcaagtc caacacggcc atcaaggggt 60
cggacaggag aaagcttcga gctgatgtga caactgcttt ccccaccctt ggaactgatc 120
aagtctctga gttagtacct ggaaaggagg agctcaacat tgtgaagttg tatgctcaca 180

aaggggatgc agtgactgtg tacgtgagtg gtggtaaccc catcctcttt gaactggaga 240
aaaatctgta tccaacagtg tacacgctgt ggtcctatcc tgatcttctg ccaaccttta 300
caacatggcc tctggtgctc gagaaactgg tagggggagc agatttgatg ctgcctggac 360
tggtgatgcc ccctgctggt ctgcctcagg tacagaaggg cgacctctgt gccatttctt 420
tggtggggaa cagagcccct gtagccattg gagttgcagc catgtccaca gctgagatgc 480
tcacgtcagg cctgaaggga a 501

<210> 183
<211> 501
<212> DNA
<213> Homo sapien

<400> 183
atctgctcac tttagcactc tggcaattaa acagaacccc cttctggcag aagcttattc 60
gaatttgggg aatgtgtaca aggaaagagg gcagttgcag gaggcaattg agcattatcg 120
acatgcattg cgtctcaaac ctgatttcat cgatggttat attaacctgg cagccgcctt 180
ggtagcagcg ggtgacatgg aaggggcagt acaagcttac gtctctgctc ttcagtacaa 240
tcctgatttg tactgtgttc gcagtgacct ggggaacctg ctcaaagccc tgggtcgctt 300
ggaagaagcc aaggcatgtt atttgaaagc aattgagacg caaccgaact ttgcagtagc 360
ttggagtaat cttggctgtg ttttcaatgc acaaggggaa atttggcttg caattcatca 420
ctttgaaaag ctgtcaccct tgacccaaac tttctggatg cttatatcaa tttaggaaat 480
gtcttgaaag agcacgcatt t 501

<210> 184
<211> 501
<212> DNA
<213> Homo sapien

<400> 184
agttctccca ggagaaagcc atgttcagtt cgagcgccaa gatcgtgaag cccaatggcg 60
agaagccgga cgagttcgag tccggcatct cccaggctct tctggagctg gagatgaact 120
cggacctcaa ggctcagctc agggagctga atattacggc agctaaggaa attgaagttg 180
gtggtggtcg gaaagctatc ataatctttg ttcccgttcc tcaactgaaa tctttccaga 240
aaatccaagt ccggctagta cgcgaattgg agaaaaagtt cagtgggaag catgtcgtct 300
ttatcgctca gaggagaatt ctgcctaagc caactcgaaa aagccgtaca aaaaataagc 360
aaaagcgtcc caggagccgt actctgacag ctgtgcacga tgccatcctt gaggacttgg 420
tcttcccaag cgaaattgtg ggcaagagaa tccgcgtcaa actagatggc agccggctca 480
taaaggttca tttggacaaa g 501

<210> 185
<211> 460
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(460)
<223> n = A,T,C or G

<400> 185
gcacaaaatg gcggcggcgg cggcggcggc tggtgctgca gggtcggcag ctcccgcggc 60
agcggccggc gccccgggat ctgggggcgc accctcaggg tcgcaggggg tgctgatcgg 120
ggacaggctg tactccgggg tgctcatcac cttggagaac tgcctcctgc ctgacgacaa 180
gctccgtttc acgccgtcca tgtcgagcgg cctcgacacc gacacagaga ccgacctccg 240
cgtggtgggc tgcgagctca tccaggcggc cggtatcctg ctccgcctgc cgcaggtggc 300
catggctacc gggcaggtgt tgttccagcg gttcttttat accaagtcct tcgtgaagca 360
ctccatggag catgtgtcaa tggcctgtgt ccacctggct tccaagatag aagangcccc 420
aagaccatac gggacgtcat caatgtgttt caccgccttc 460

<210> 186
<211> 401
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(401)
<223> n = A,T,C or G

<400> 186
cgtgttttgg gccggttctg gagtggctgg cggcggggcc tgggtgtccg cccagtgccc 60
gaggacgcag gctttggcac cgaagcccgg catcagaggc aaccccgcgg ctcctgccaa 120
cggtcggggc ccctcgggga ccagcccttc gcggggctgc tgccaaaaaa cctcagtcgg 180
gaggagctgg ttgatgcgct gcgggcagcc gtggtggacc ggaaaggacc tctagtgacg 240
ttgaacaagc cacagggtct accagtgaca ggaaaaccag gagagctgac gttgttctca 300
gtgctgccag agctgagcca gtccctangg ctcagggagc aggagcttca ggttgtccga 360
ncatctggga agtaagtggt angggtgaca ggaagctang a 401

<210> 187
<211> 376
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(376)
<223> n = A,T,C or G

<400> 187
gcatccgccc tgtctgggag gtgggggggcg cgcctctgnc cagccgccac gtctgggaag 60
tggggagccc cactgcccgg ctgccacccc gtctgggagg tgtacccaac agctcattga 120
gaacgggcca tgatgacgat ggcggttttg tcgaatagaa aaggggaaa tgtggggaaa 180
agaaagagag atcagattgt tactgtgtct gtgtagaaag aagtagacat aggagactcc 240
attttgttct gtactaagaa aaattcttct tccttgggat gctgttaatc tataacctta 300
cccccaaccc cgtgctctct gaaacatatg ctgtgtcaac tcagggttaa atggattaag 360
ggcggtgcaa gatgtg 376

<210> 188
<211> 376
<212> DNA
<213> Homo sapien

<400> 188
aacctggagc gcaccttcat cgccatcaag ccggacggcg tgcagcgcgg cctggtgggc 60
gagatcatca agcgcttcga gcagaaggga ttccgcctcg tggccatgaa gttcctccgg 120
gcctctgaag aacacctgaa gcagcactac attgacctga aagaccgacc attcttccct 180
gggctggtga agtacatgaa ctcagggccg gttgtggcca tggtctggga ggggctgaac 240
gtggtgaaga caggccgagt gatgcttggg gagaccaatc cagcagattc aaagccaggc 300
accattcgtg gggacttctg cattcaggtt ggcaggaaca tcattcatgg cagtgattca 360
gtaaaaagtg ctgaaa 376

<210> 189
<211> 501
<212> DNA
<213> Homo sapien

<400> 189
cccctaccgc ggagcagcac catgtcggcg ccggcggcca aagtcagtaa aaaggagctc 60

aactccaacc acgacggggc cgacgagacc tcagaaaaag aacagcaaga agcgattgaa 120
cacattgatg aagtacaaaa tgaaatagac agacttaatg aacaagccag tgaggagatt 180
ttgaaagtag aacagaaata taacaaactc cgccaaccat tttttcagaa gaggtcagaa 240
ttgatcgcca aaatcccaaa tttttgggta acaacatttg tcaaccatcc acaagtgtct 300
gcactgcttg gggaggaaga tgaagaggca ctgcattatt tgaccagagt tgaagtgaca 360
gaatttgaag atattaaatc aggttacaga atagattttt attttgatga aaatccttac 420
tttgaaaata aagttctctc caaagaattt catctgaatg agagtggtga tccatcttcg 480
aagtccaccg aaatcaaatg g 501

<210> 190
<211> 501
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(501)
<223> n = A,T,C or G

<400> 190
aagttctgaa gattcatttt tgtctgccat tataaattat actaatagct ctacagtcca 60
ctttaagttg tcccctacat atgtattata tatggcatgc cggtatgtat tgtccaacca 120
gtacagacct gacatcagcc ctacagagcg cacacataaa gtcattgcag tcgtcaacaa 180
gatggtgagc atgatggagg gtgtcatcca gaaacagaag aatattgcag gggcacttgc 240
cttctggatg gcaaatgcat ctgaacttct caacttcatt aagcaagacc gagaccttag 300
tcggatcaca ctggatgctc aagatgtttt agcacatttg gttcaaatgg catttaaata 360
cttggttcac tgtcttcaat cagaacttaa taattacatg ccagcctttc tagatgaccc 420
tgaagagaac agtctgcaac gaccaaaaat agatgatgtg ctgcacacgc tcacaggagc 480
catgtncttg ctacgacgct g 501

<210> 191
<211> 501
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(501)
<223> n = A,T,C or G

<400> 191
ttgtgcgtgc tcagccacta ccctttcttn gnccactttc cganagtgtt tgtatactct 60
caagcgcctg gnggactgct gtagtgagcg ccttctgggc aagaaactgg gcatccctcg 120
aggcgtacaa agggacacca tgtggcggat ctttactgga tcgctgctgg tagaggagaa 180
gtcaagtgcc cttctgcatg accttcgaga gattgaggcc tggatctatc gattgctgcg 240
ctccccagta cccgtctctg ggcagaagcg agtagacatc gaggtcctac cccaagagct 300
ccagccagct ctgacctttg ctcttccaga cccatctcga ttcaccctag tggatttccc 360
actgcacctt cccttggaac ttgtaggtgt ggacgcctgt ctccagntgc taacctgcat 420
tctggtagag cacaaggcgg cgctacagtc ccgagactac aatgcactct ccatgtctgt 480
gatggcatnc atggcaatga t 501

<210> 192
<211> 501
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(501)

<223> n = A,T,C or G

<400> 192
tttganttga accagaagct ccaggaagaa aaacataaaa gcataactga ggcacttagg 60
agacaggagc agaatataaa gagttttgag gagacctatg accgaaagct caagaatgaa 120
cttctaaact tccacaggct gcatggtgtc tgcctggctt tgggaatcct catatgactt 180
tggcaggtgt tggagtttgg aggctcttcg ccacaggagt gcttctattt ccttttggaa 240
ccaaaagggc agctggtaac agctgggaaa gggaagtgaa actgtgaaaa tgtgcctttt 300
ggtattgcta atccggatat aatgctcttg gcagttggct ctcaggactg tgcttagtcc 360
ctgagcacaa aagttcttac cttggttggg ggtgggcaga tggtacaggt ggattggaag 420
tgaccgtctg attatcattt gggattgagt ctgttgtgtg ctgtgtaaat ttaatttacc 480
cctttgctct ttgtgtcagt t 501

<210> 193
<211> 501
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(501)
<223> n = A,T,C or G

<400> 193
agnttctcgc tctcgcctgc ctgcccgctc ccttgcttgc tcgcgctttc gctcgccctc 60
tcctcgagga tcgaggggac tctgaccaca gcctgtggct gggaagggag acagaggcgg 120
cggcggctca ggggaaacga ggctgcagtg gtggtagtag gaagatgtcg ggcgaggacg 180
agcaacagga gcaaactatc gctgaggacc tggtcgtgac caagtataag atgggggcg 240
acatcgccaa cagggtactt cggtccttgg tggaagcatc tagctcaggt gtgtcggtac 300
tgagcctgtg tgagaaaggt gatgccatga ttatggaaga aacagggaaa atcttcaaga 360
aagaaaagga aatgaagaaa ggtattgctt ttcccaccag catttcggta aataactgtg 420
tatgtcactt ctccccttg aagagcgacc aggattatat tctcaaggaa ggtgacttgg 480
taaaaattga ccttggggtc c 501

<210> 194
<211> 560
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(560)
<223> n = A,T,C or G

<400> 194
ggcttcactc tcacaaactc cttgaatttc ttctctttat tcttttcctt gtcttttgta 60
gttggggaac tggcanagac ccgcttcctg gtcagggtct cctggctggg cttgtctgaa 120
gctgaagggc ccctggtttg gacatgcctc tttcccgggc tctcttctgg ctccagtgac 180
ttctccattc catggaaata cttcatgtga tagtgcaaca gtttggcttt gcggaaaaat 240
tttaaacagt ccacaacttt gcatctaaac ttatggtcta ggtcgacagc tggtgcatta 300
natgacccaa aatcatctgt tttcttaaaa gtatttgtta cttccacagt cgaaatctct 360
tgtaattcca caaggggaga agtcggttct gttttcatcg tgttttctcc cattgatggg 420
cagttcaact ccaagcctgc agccccggat ccatccccaa aggagnggca agtcagtgca 480
natganacct ggccagcttc caaagcagac ttcaactgac cttcttcaga ttccttggta 540
ctanacaacg tgtcttgcaa 560

<210> 195
<211> 582
<212> DNA

<213> Homo sapien

<400> 195
ggcacctggg gagaaatgga tggagaaggg acctggctgg aaagcctttg ccccgctgct 60
ctgctccgcc cataagagga cccctgaaat gtcccgtgca gtttgttcaa gtcccctgtg 120
tgatgaaatg tgcctctcgc cttacccgtg tgagaatacc tgtggtgtgg cagcgagtat 180
tttggtattt gacctgtcca aagacgactt gatacctcta taatgtaaca gaaaaggtca 240
gaaaatatta agcaagtaga agtgtggagc atattaagca agatgaacat ctcgggaagc 300
agctgtggaa gccctaactc tgcagataca tctagtgact ttaaggacct ttggacaaaa 360
ctaaaagaat gtcatgatag agaagtacaa ggtttacaag taaaagtaac caagctaaaa 420
caggaacgaa tcttagatgc acaaagacta gaagaattct tcaccaaaaa tcaacagctg 480
agggaacagc agaaagtcct tcatgaaacc attaaagttt tagaagatcg gttaagagca 540
ggcttatgtg atcgctgtgc agtaactgaa gaacatatgc gg 582

<210> 196
<211> 401
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(401)
<223> n = A,T,C or G

<400> 196
aaaccaaaga atggattgaa gagaagaatc aagctctaaa cacagacaat tatggacatg 60
atctcgccag tgtccaggcc ctgcaacgca agcatgaggg cttcgagagg gaccttgcgg 120
ctctcggtga caaggtaaac tcccttggtg aaacagcaga gcgcctgatc cagtcccatc 180
ccgagtcagc agaagacctg caggaaaagt gcacagagtt aaaccaggcc tggagcagcc 240
tggggaaacg tgcagatcag cgcaaggcaa agttgggtga ctcccacgac ctgcagcgct 300
tccttagcga tttccgggac ctcatgtctt ggatcaatgg aatacggggg ttggtgtcct 360
cagatgagct anccaaggat gtcaccggag ctgangcatt g 401

<210> 197
<211> 457
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(457)
<223> n = A,T,C or G

<400> 197
agtttcccgg accatggcca acctggagcg caccttcatn gccatcaagc cggacggngt 60
gcancgcggc ctggtgggcg agatcatcaa gcgcttngan cagaagggat tccgcctcnt 120
ggccatgaan ttcctccggg cctctgaana acacctgaag cagcactaca ttgacctgaa 180
agaccgacca ttcttccctg ggctggtgaa ntacatgaac tcagggccgg ttgtggccat 240
ggtctgggag gggctgaacg tggtgaagac aggccgagtg atgcttgggg agaccaatcc 300
agnagattca aagccaggca ccattcntgg ggacttctgc attcaggttg gnangaacat 360
nattcatggn agtgattcan taaaaagtgc tgaaaaanaa atcancctat ggnttaagcc 420
tgaagaactg gttgactaca agtcttgngc tcatgac 457

<210> 198
<211> 474
<212> DNA
<213> Homo sapien

<400> 198

aggctgaacc cgaggagatg aacccttaa ctaaggtgaa gctgatcaac gagctgaatg 60
aacgagaggt ccagcttggg gtggccgata aggtgtcctg gcactccgag tacaaggaca 120
gcgcctggat cttcctggga gggcttcctt atgaactgac tgaaggggac atcatctgtg 180
tgttctcaca atatggggag attgttaaca ttaatctcgt gcgggacaag aaaactggga 240
aatccaaagg attctgtttc ctctgctatg aagaccagag gagcacaatt ctggccgtcg 300
acaattttaa tgggatcaag atcaaaggaa gaactatccg agtggatcat gtgtctaact 360
atcgggctcc taaggactca gaagaaatag atgatgtgac cagacaactc caggagaagg 420
gctgtggggc tcgtaccccc tcaccaagtt tgtctgagag ctctgaagat gaaa 474

<210> 199
<211> 574
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(574)
<223> n = A,T,C or G

<400> 199
gagaagaaac aggaagaaga agaaacgatg cagcaagcga catgggtaaa atacacattt 60
ccagttaagc atcaggtttg gaaacaaaaa ggtgaagagt acagagtgac aggatatggt 120
ggttggagct ggattagtaa aactcatgtt tataggtttg ttcctaaatt gccaggcaat 180
actaatgtga attacagaaa gtcgttagaa ggaaatgtga aggagctctt agattctgac 240
agtgataaac cctgcaagga agaaccaatg gaagtagacg atgacatgaa aacagagtca 300
catgtaaatt gtcaggagag ttctcaagta gatgtggtca atgttagtga gggttttcat 360
ctaaggacta gttacaaaaa gaaaacaaaa tcatccaaac tagatggact tcttgaaagg 420
agaattaaac agtttacact ggaagaaaaa cagcgactcg aaaaaatcaa gttggagggt 480
ggaattaagg gtataaggaa agacttctac aaattcttca aaaaatctct ctgaatcacc 540
agtaataacc gaaagcaaaa gaanggtgtc agag 574

<210> 200
<211> 522
<212> DNA
<213> Homo sapien

<400> 200
tccataacct tatggagaga aaggactttg agacatggct tgataacatt tctgttacat 60
ttctttctct gacggacttg cagaaaaatg aaactctgga tcacctgatt agtctgagtg 120
gggcagtcca gctcaggcat ctctccaata acctagagac tctcctcaag cgggacttcc 180
tcaaactcct tcccctggag ctcagttttt atttgttaaa atggctcgat cctcagactt 240
tactcacatg ctgcctcgtc tctaaacagt ggaataaggt gataagtgcc tgtacagagg 300
tgtggcagac tgcatgtaaa aatttgggct ggcagataga tgattctgtt caggacgctt 360
tgcactggaa gaaggtttat ttgaaggcta ttttgagaat gaagcaactg gaggaccatg 420
aagcctttga aacctcgtca ttaattggac acagtgccag agtgtatgca ctttactaca 480
aagatggact tctctgtaca gggtcagatg acttgctgca aa 522

<210> 201
<211> 501
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(501)
<223> n = A,T,C or G

<400> 201
atctccgcct ggttcggccc gcctgcctcc actcctgcct ctaccatgtc catcagggtg 60

acccagaagt cctacaaggt gtccacctct ggccccggg ccttcagcag ccgctcctac 120
acgagtgggc ccggttcccg catcagctcc tcgagcttct cccgagtggg cagcagcaac 180
tttcgcggtg gcctgggcgg cggctatggt ggggccagcg gcatgggagg catcaccgca 240
gttacggtca accagagcct gctgagcccc cttgtcctgg aggtggaccc caacatccag 300
gccgtgcgca cccaggagaa ggagcagatc aagaccctca acaacaagtt tgcctccttc 360
atagacaagg tacggttcct ggagcancag aacaagatgc tggagaccaa gtggagcctt 420
cttgcagcag cagaagacgg ctcgaagcaa catggacaac atgttcnaaa gctacatcaa 480
caaccttagg cgnagcttga a 501

<210> 202
<211> 501
<212> DNA
<213> Homo sapien

<400> 202
gcgttctgtg gagagagtgc gaggtcaggc catgaacttg ggagatggtt taaagcttga 60
aactaaatta ctggatggaa aaaccaagct aatattgtct ccatatgaac ataaatcaaa 120
aatttctgtg aagatgggaa ataaggccaa gattgcaaaa tgtcctttaa gaacaaaaac 180
tgggcacatt ctaaaatcaa cacaagatac ttgtattggg agtgaaaaac ttttgcaaaa 240
gaagccagtt ggttcagaaa catcacaggc aaaaggtgaa aaaaatggaa tgacttttc 300
atccactaag gatttatgta aacaatgtat agataaagac tgtcttcata tccagaaaga 360
gatttcacct gcaactccta atatgcagaa gactagaaac accgtaaata catctctagt 420
aggtaaacag aagcctcaca aaaaacacat cacagctgaa aacatgaaga gcagtttggt 480
gtgtctaaca caagaccaac t 501

<210> 203
<211> 395
<212> DNA
<213> Homo sapien

<400> 203
cttcatcatt gcagactcct tcctacatca tgcgtatcgt tttcattata cactttgtgc 60
cactttgctg ctagccttca agggattgca cagctacttc attacagtaa cagaagagat 120
tccttcttgt cagaaactag aactggccaa ggccaacatg cagctcctat atgagcgtct 180
tctcagaaga aaacagctac gaacacagaa agacaaccat ctagaggaaa tggatgtaga 240
agctcgactt actgaactat gtgaagaagt taagaaaata gagaatcctg atgaactggc 300
agaacttata aatatgaatc ttgcgcaact ttgctcactt ttgatggctt tatggggaca 360
gtttctggaa gttataacgc tacacgaaga actaa 395

<210> 204
<211> 501
<212> DNA
<213> Homo sapien

<400> 204
aggtcaggca gaaattggag agggggctca aaagctgctg cggcccaaca gcttgagact 60
ggcaagtgac tcagatgcag agtcagactc tcgggcaagc tctcccaact ccaccgtctc 120
caacaccagc accgagggct tcgggggcat catgtctttt gccagcagcc tctatcggaa 180
ccacagtacc agcttcagtc tttcaaacct cacactgccc accaaaggtg cccgagagaa 240
ggccacgccc ttccccagtc tgaaaggaaa caggagggcg ttagtggatc agaagtcatc 300
tgtcattaaa cacagcccaa cagtgaaaag agaacctcca tcaccccagg gtcgatccag 360
caattctagt gagaaccagc agttcctgaa ggaggtggtg cacagcgtgc tggacggcca 420
gggagttggc tggctcaaca tgaaaaaggt gcgccggctg ctggagagcg agcagctgcg 480
agtctttgtc ctgagcaagc t 501

<210> 205
<211> 501
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(501)
<223> n = A,T,C or G

<400> 205
cagaagtgca gcggtggcgg cggctggttg cgggccggcg gcgggctggc ggagatggag 60
gatcttgttc aagatggggt ggcttcacca gctacccctg ggaccgggaa atctaagaat 120
tggagaaaga aattgaagaa ctcagatcaa aacctgttac tgaaggaact ggtgatatta 180
ttaaggcatt aactgaacgt ctggatgctc ttcttctgga aaaagcagag actgagcaac 240
agtgtctttc tctgaaaaag gaaaatataa aaatgaagca agaggttgag gattctgtaa 300
caaagatggg agatgcacat aaggagttgg aacaatcaca tataaactat gtgaaagaaa 360
ttgaaaattt gaaaaatgag ttgatggcag tacgttccaa atacagtgaa gacaaagcta 420
acttacaaaa ncagctggaa naagcaatga atacncaatt agaactttca naacaactta 480
aatttcanaa caactctgaa g 501

<210> 206
<211> 599
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(599)
<223> n = A,T,C or G

<400> 206
tggtcgcacc agctctctgc tctcccagcg cagcgccgcc gcccggcccc tccagcttcc 60
cggaccatgg ccaacctgga gcgcaccttc atcgccatca agccggacgg cgtgcagcgc 120
ggcctggtgg gcgagatcat caagcgcttc gagcagaagg gattccgcct cgtggccatg 180
aagttcctcc gggcctctga agaacacctg aagcagcact acattgacct gaaagaccga 240
ccattcttcc ctgggctggt gaagtacatg aactcagggc cggttgtggc catggtctgg 300
gaggggctga acgtggtgaa gacaggccga gtgatgcttg gggagaccaa tccagcagat 360
tcaaagccag gcaccattcg tggggacttc tgcattcagg ttggcaggaa catcattcat 420
ggcagtgatt cagtaaaaag tgctgaaaaa gaaatcagcc tatggtttaa gcctgaagaa 480
ctggttgact acaagtcttg tgctcatgac tgggtctatg aataagaggt ggacacaaca 540
gcagtctcct tcacacggcg tggtgtgtcc tggacacagt nttattcttg acttaaagc 599

<210> 207
<211> 395
<212> DNA
<213> Homo sapien

<400> 207
ccggccgggc cgagggtcgg cggccgccgg cgggccgggc ccgcgcacag cgcccgcatg 60
tacaacatga tggagacgga gctgaagccg ccgggcccgc agcaaacttc ggggggcggc 120
ggcggcaact ccaccgcggc ggcggccggc ggcaaccaga aaaacagccc ggaccgcgtc 180
aagcggccca tgaatgcctt catggtgtgg tcccgcgggc agcggcgcaa gatggcccag 240
gagaacccca agatgcacaa ctcggagatc agcaagcgcc tgggcgccga gtggaaactt 300
ttgtcggaga cggagaagcg gccgttcatc gacgaggcta agcggctgcg agcgctgcac 360
atgaaggagc acccggatta taaataccgg ccccg 395

<210> 208
<211> 398
<212> DNA
<213> Homo sapien

<400> 208

aggctctcca agccctgctg ttatattttt ccaggaggga ggggcgattc tgccttgttt 60
gcagtgaatg gtttcaatat gctcatcaat ggcggatcag agagaaaatc ctgcttctgg 120
aagctcatcc gacacttaga ccgagtggac tccatcctgc tcacccacat tggggatgac 180
aatttgcctg gaataaacag catgttacag cggaaaattg cagagctcga ggaagaacag 240
tcccagggct ccaccacaaa tagtgactgg atgaaaaacc tcatctcccc tgacttagga 300
gttgtatttc tcaatgtacc tgaaaatctc aaaaatccag agccaaacat caagatgaag 360
agaagcatag aagaagcctg cttcactctc cagtacct 398

<210> 209
<211> 501
<212> DNA
<213> Homo sapien

<400> 209
gcgcagcctc ctgggagttg tagtcgcgat cctgaggtaa cggataagtt tataccatgg 60
atagcacaaa ggagaagtgt gacagttaca aagatgatct tctgcttagg atgggactta 120
atgataataa agcaggaatg gaaggattag ataaagagaa aattaacaaa attataatgg 180
aagccacgaa ggggtccaga ttttatggaa atgagctcaa gaaagaaaag caagtcaacc 240
aacgaattga aaatatgatg caacaaaaag ctcaaatcac cagccaacag ctaagaaaag 300
cacaattaca ggttgacaga tttgcaatgg aattagaaca aagccgaaat ttgagcaata 360
ccatagtgca cattgacatg gatgctttct atgcagctgt agaaatgagg gacaatccag 420
aattgaagga taaacccatt gctgtaggat caatgagtat gctgtctact tcaaattacc 480
atgcaaggag atttggtgtt c 501

<210> 210
<211> 450
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(450)
<223> n = A,T,C or G

<400> 210
cggaacaagt gcagaacagg ataatcggtt cagcaacaaa cagaagaaac tactgaagca 60
gctgaaattt gcagaatgcc tagaaaaaaa ggtggacatg agcaaagtaa atttggaggt 120
tataaagcct tggataacaa aaagagtaac ggaaatcctt gggtttgaag atgatgttgt 180
gattgagttt atattcaacc agctggaagt gaagaatcca gactccaaaa tgatgcaaat 240
caacctgact ggatttttga atggaaaaaa tgctcgagaa tttatgggag aactgtggcc 300
cctgctgcta agtgcacaag aaaacatcgc gggaatccct tctgctttcc tagaactgaa 360
gaaagaagaa ataaaacaaa gacagattga acaagaaaaa ctggcatcta tgaaaaagcn 420
agatgaagac caagattaaa gagaaangga 450

<210> 211
<211> 601
<212> DNA
<213> Homo sapien

<400> 211
ctcagagcag ctggaacagg ccaagcggtt caaagcaaat ctagagaaga acaagcaggg 60
cctggagaca gataacaagg agctggcgtg tgaggtgaag gtcctgcagc aggtcaaggc 120
tgagtctgag cacaagagga agaagctcga cgcgcaggtc caggagctcc atgccaaggt 180
ctctgaaggc gacaggctca gggtggagct ggcggagaaa gcaagtaagc tgcagaatga 240
gctagataat gtctccaccc ttctggaaga agcagagaag aagggtatta aatttgctaa 300
ggatgcagct agtcttgagt ctcaactaca ggatacacag gagcttcttc aggaggagac 360
acgccagaaa ctaaacctga gcagtcggat ccggcagctg gaagaggaga agaacagtct 420
tcaggagcag caggaggagg aggaggaggc caggaagaac ctggagaagc aagtgctggc 480
cctgcagtcc cagttggctg ataccaagaa gaaagtagat gacgacctgg gaacaattga 540

aagtcttgga agaagccaag aagaacttct gaaggacgcg gaggccctga gccaacgcct 600
g 601

<210> 212
<211> 498
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(498)
<223> n = A,T,C or G

<400> 212
atgacaaata ttccacatct gtgattctct ccagtcaaaa gttctttgag acgatgccat 60
cggccttggc caatcggaga atggaatcat ctgactcacc catcctacga atggccccgc 120
agatagcata agttttaaac tggccattaa acctgcctgt gaccttgtca acctcggcca 180
cgttcatctg gatggatgcg tggtccttgg caccgatgat gcgattgcta gcggagcatt 240
tccgcggcac gtacaggtcc acgaactcgc cggcgtcgtt ctgcatttcg aggctgggct 300
gcgcctgctg ccactcgtgc cgaattcttt ggatccacta gtgtcgacct gcaggcgcgc 360
gagctccagc ttttgtccct ttagtgaggg ttaatttcga gcttggcgta atcaanggca 420
tagctggttc ctgngngaaa ttggtatccg tcacaattcc ncncaatata cgagccggaa 480
gtataaaggg naaagcct 498

<210> 213
<211> 601
<212> DNA
<213> Homo sapien

<400> 213
actaccagac aaccttagcc aaaccattta cccaaataaa gtataggcga tagaaattga 60
aacctggcgc aatagatata gtaccgcaag ggaaagatga aaaattataa ccaagcataa 120
tatagcaagg actaacccct ataccttctg cataatgaat taactagaaa taactttgca 180
aggagagcca aagctaagac ccccgaaacc agacgagcta cctaagaaca gctaaaagag 240
cacacccgtc tatgtagcaa aatagtggga agatttatag gtagaggcga caaacctacc 300
gagcctggtg atagctggtt gtccaagata gaatcttagt tcaactttaa atttgcccac 360
agaaccctct aaatcccctt gtaaatttaa ctgttagtcc aaagaggaac agctctttgg 420
acactaggaa aaaaccttgt agagagagta aaaaatttaa cacccatagt aggcctaaaa 480
gcagccacca attaagaaag cgttcaagct caacacccac tacctaaaaa atcccaaaca 540
tatactgaac tcctcaaccc aattggccaa tctatcccct atagaagact aatggtagta 600
t 601

<210> 214
<211> 500
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(500)
<223> n = A,T,C or G

<400> 214
aggctgcatt tacggggtct cccggagggc cagagtcgtg gcttacagaa gagacgaaat 60
gtggtctgag ggacgatatg aatatgaaag aattccgaga gaacgagcac ctcctcgaag 120
tcatcccagt gatgaatctg gttatagatg gacaagagac gatcattctg caagcaggca 180
acctgaatac agggacatga gagatggctt tagaagaaaa agtttctact cttcccatta 240
tgcgagagag cggtctcctt ataaaaggga caatactttt ttcagagaat cacctgttgg 300
ccgaaaggat tctccacaca gcanatctgg ttccagtgtc agtagcanaa gctctctcca 360

gaaaggagca aatcatactc tttccatcag tctcaacata gaaataaaga gaggcctgtc 420
agtctttgaa aacatcaaga gatacttccc ctcaagtggt tcacagttct tctcaaaggg 480
gtagacaaac ccagtaggta 500

<210> 215
<211> 501
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(501)
<223> n = A,T,C or G

<400> 215
gcctgtggga gcccgtggcc tttaaagtgc cgttcagcct tttcctccag gggtgctttg 60
taaacacggc tgtgctcagg gctcgcgggt gaccgaaagg atcatgaact agtgacctgg 120
aaagggtact agatggaaac ttgagaaagg actgcttatt gataacagct aaggtattcc 180
tggaagcaga gtaaataaag ctcatggccc accagctaga aagtattctt gccatgagaa 240
aaagaatgtg ataagttatt caacttatga aattcaagtt acatgtgaat tctgccaggc 300
aatacaagga cctgtggaat atgagtgatg acaaaccctt tctatgtact gcgcctggat 360
gtggccagcg ttttaccaac gaggatcatt tggctgtcca taaacataaa catgagatga 420
cactgaaatt tggtccanca cgtaatgaca gtgtcattgt ggctgatcag accccaacac 480
caacaagatt cttgaaaaac t 501

<210> 216
<211> 501
<212> DNA
<213> Homo sapien

<400> 216
aggcggcctt gggggcatct gcattggagt tgggggtgcc gatgctgtgg atgtcatggc 60
tgggatcccc tgggagttga agtgccccaa ggtgattggc gtgaagctga cgggctctct 120
ctccggttgg tcctcaccca aagatgtgat cctgaaggtg gcaggcatcc tcacggtgaa 180
aggtggcaca ggtgcaatcg tggaatacca cgggcctggt gtagactcca tctcctgcac 240
tggcatggcg acaatctgca acatgggtgc agaaattggg gccaccactt ccgtgttccc 300
ttacaaccac aggatgaaga agtacctgag caagaccggc cgggaagaca ttgccaatct 360
agctgatgaa ttcaaggatc acttggtgcc tgaccctggc tgccattatg accaactaat 420
tgaaattaac ctcagtgagc tgaagccaca catcaatggg cccttcaccc ctgacctgct 480
caccctgtgg cagaagtggg c 501

<210> 217
<211> 408
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(408)
<223> n = A,T,C or G

<400> 217
gctacacctg gacgtgacgt ggggctggga gcactggggc gggatcctgc cacagtcgct 60
ggacctgttg ctctgcatca acatggccca tgtcagcccc ctgcgctgca cggaggaacc 120
cagaatgggg gcttcgggac acagccctcc tggaggacct gggaaaggcc agtggcctgc 180
tcctggagag gatggtggac atgccagcca acaacaaatg cctgatcttc cggaaaaact 240
aagcccctcc ttcacccccg cacacctgca tccctgccgg angctctgtg aggcacgaac 300
cctgcctccc taggccggac cttgtggacg acagccccac ccagtctgtg ctctcagccg 360
ntggccgaag ggcccancct gctcagaata aacatgtcct gctgccgg 408

<210> 218
<211> 402
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(402)
<223> n = A,T,C or G

<400> 218
tgcttgtctc aaagattaag ccatgcatgt ctaagtacgc acggccggta tcctgctccg 60
cctgccgcag gnggccatgg ntaccgggca ggngttgttc cagcggttct tttataccaa 120
gtccttcgtg aagcactcca tggagcatgt gtcaatggcc tgtgtccacc tggctttcaa 180
gatagaagag gccccaagac gcatacggga cgtcatcaat gtgtttcacc cgccttcgac 240
agctgagaga caaaaagaag cccgtgcctc tactactgga tcaagattat gttaatttaa 300
agaacccaat tataaaggcg ggnaagacna ttcttcaaaa agatgggntt ctgcgnccat 360
gtgaagcatn ctcataagan aatcgntatg taccttcagg gg 402

<210> 219
<211> 486
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(486)
<223> n = A,T,C or G

<400> 219
aatgctgcgg agattgaggt gtcggttcgt gctgctgagc tgcccaggct tcacggagcg 60
gtgttggaaa tcaatagctc ttctagcctt tgcattgttt aaatataata gtgtcattgg 120
actaagatgt tcctgatgcc aacctcttca gagttaaaca gtgggcagaa cttcctaacc 180
cagtggatga ccaatccttc tcgggctggg gtcatattaa atcgtggatt tcctattttg 240
gaagcagaca aagagaagcg agcagcttgt ggacatttct accagctttt nctattaaaa 300
ggcacacatt tttctgatag cttcagcttt tataaatgaa gaaaaattca cttcttgaag 360
aacagaagtt ggagtcaaac aacacttaca aaccacagtc agataaatct gaaacccata 420
cagcctttcc ttgcattaaa aagggaccnc aggtngcggn atggtccagt gctcctggac 480
ncccgg 486

<210> 220
<211> 380
<212> DNA
<213> Homo sapien

<400> 220
ggcggattag ccttcgcggg gcaaaatgga gctcgaggcc atgagcagat ataccagccc 60
agtgaaccca gctgtcttcc cccatctgac cgtggtgctt ttggccattg gcatgttctt 120
caccgcctgg ttcttcgttt acgaggtcac ctctaccaag tacactcgtg atatctataa 180
agagctcctc atctccttag tggcctcact cttcatgggc tttggagtcc tcttcctgct 240
gctctgggtt ggcatctacg tgtgagcacc caagggtaac aaccagatgg cttcactgaa 300
acctgctttt gtaaattact ttttttact gttgctggaa gtgtcccacc tgctgctcat 360
aataaatgca gatgtatagc 380

<210> 221
<211> 406
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(406)
<223> n = A,T,C or G

<400> 221
gcggattagc cttcgcgggg caaaatggag ctcgaggcca tgagcagata taccagccca 60
gtgaacccag ctgtcttccc ccatctgacc gtggtgcttt tggccattgg catgttcttc 120
accgcctggt tcttcgttta cgangtcacc tctaccaagt acactcgtga tatctataaa 180
gagctcctca tctccttagt ggcctcactc ttcatgggct ttggagtcct cttcctgctg 240
ctctgggttg gcatctacgt gtgagcaccc aagggtaaca accagatggc ttcactgaaa 300
cctgcttttg taaattactt ttttttactg ttgctggaag tgtcccacct gctgctcata 360
ataaatgcag atgtatagcc ctatagngag cgtattacaa ttcact 406

<210> 222
<211> 501
<212> DNA
<213> Homo sapien

<400> 222
aatggcggta gttggtgtgt cctcggtttc tcggctgctg ggtcggtccc gcccacagct 60
ggggcggcct atgtcgagtg gcgcccatgg cgaagagggc tcagctcgca tgtggaagac 120
tctcaccttc ttcgtcgcgc tccccggggt ggcagtcagc atgctgaatg tgtacctgaa 180
gtcgcaccac ggagagcacg agagacccga gttcatcgcc tacccccatc tccgcatcag 240
gaccaagccg tttccctggg gagatggtaa ccatactcta ttccataacc ctcatgtgaa 300
tccacttcca actggctacg aagatgaata aagagaatct ggaccactac ccgggcacca 360
gggaccacag cactggtttg gaccgttact ctgcacatgg accagaaaaa gtatatggga 420
ccttaagctc accttcttta cttgtatcaa atgatgactg gtatactggt ctcccatccc 480
tttgcttgtg gcaggagatg g 501

<210> 223
<211> 455
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(455)
<223> n = A,T,C or G

<400> 223
aatcttatgc aaaagggaca caggggttca aaaataaaaa tttctcttcc ccctccccaa 60
acctgtaccc cagctccccg accacaaccc ccttcctccc ccggggaaag caagaaggag 120
caggtgtggc atctgcagct gggaananag aggccgggga ggtgccgagc tcggtgctgg 180
tctctttcca aatataaata cgtgtgtcan aactggaaaa tcctccagca cccaccaccc 240
aagcactctc cgttttctgc cggtgtttgg agaggggcgg ggggcagggg cgccaggcac 300
cggctggctg cggtctactg catccgctgg gtgtgcaccc cgcgagcctc ctgctgctca 360
ttgtagaaga gatgacactc ggggtccccc ccggatggng ggggctccct ggatcagctt 420
tccggnggnt ggggttcaca caccagcact tccca 455

<210> 224
<211> 507
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(507)

<223> n = A,T,C or G

<400> 224
ttacccacac ccattgtagc ccttgggtgn gggatgtgcc ctgtccctgc agggccaaaa 60
gggtccatgt ttccctcaaa tctcaaagca gtcctggccc aggctgcagg caggagggaa 120
gtcgtgacct cttggcaggc tcagtcctgc agctgcccca agcagccana ctgtccctgg 180
ggctcgtcca ggcccgggcg ctggctggga ggggaggtgt ctggcaggtc ttggcatgga 240
ggaaaanagc tgctgcaggg cctntcgggg gaggggttgg ccaagtaggc attcaccagc 300
tgcatgatct cttccacctg ggggctctgc aggaggagct ggntctctcc caccctcaag 360
gccagggtgn gggggcccat tagctggcag gcggccacat ggccatagct gacactgngg 420
atgggctccg tctcccctgg ccggganagg gacatggcct tggctcccaa gcccaggcac 480
agtttntggg ggagcacccc gaccagg 507

<210> 225
<211> 572
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(572)
<223> n = A,T,C or G

<400> 225
aaacctccct taaagattct ttgatgcttt gctctatcac tgtanacctg gtctttttcc 60
ccccagtttt ttctttttta cattctgggt tgctattttc anattaataa tttgatgacc 120
ccatcacagt accaaaatac cccccaaaat gaagttcaaa tttgatcaaa acataaatca 180
gagngagnga gtaaaattat aaaggccagg cagcaggaaa agtcaccctc aactaccatn 240
tgactggtca ggtctcaccc atgccaaggg gggcaggaag agganaaatc tattatacat 300
gcaacactga actggggaac atggcttggg gcctccagga cagttcaggt ccccaagcta 360
acccccctact tcccanacag ctgctcgtac agtttgggca catagtcatc ccactcggcc 420
tggtaacacg tgccagccac cggggccctg agctcatact ttttacggaa ggacgccacc 480
ttgaatttgc cacggnggnc tccanancgg ttgctgaaga tgggctcntc acactttagc 540
gggctgtcct gctcgtaaac canccaaaca ta 572

<210> 226
<211> 401
<212> DNA
<213> Homo sapien

<400> 226
gaagcgtctc cgttgggtcc ggccgctctg cgggactctg aggaaaagct cgcaccaggt 60
ggacgcggat ctgtcaacat gggtaaagga gaccccaaca agccgcgggg caaaatgtcc 120
tcgtacgcct tcttcgtgca gacctgccgg gaagagcaca agaagaaaca cccggactct 180
tccgtcaatt tcgcggaatt ctccaagaag tgttcggaga gatggaagac catgtctgca 240
aaggagaagt cgaagtttga agatatggca aaaagtgaca aagctcgcta tgacagggag 300
atgaaaaatt acgttcctcc caaaggtgat aagaagggga agaaaaagga ccccaatgct 360
cctaaaaggc caccatctgc cttcttctgt tttgctctga a 401

<210> 227
<211> 501
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(501)
<223> n = A,T,C or G

<400> 227
agcgcttcta gaaatgctga gccgattatc aggattagca aatgttgttt tgcatgaatt 60
atcaggagat gatgacactg atcagaatat gagggctccc ctagaccctg aattacacca 120
agaatctgac atggaattta ataatactac acaagaagat gttcaggagc gcctggctta 180
tgcagagcaa ttggtggtgg agctaaaaga tattattaga cagaaggatg ttcaactgca 240
gcagaaagat gaagctctac aggaagagag aaaaagctgt gatacaaaat taaaaaacta 300
aacttctgcg aaggccaatt acttctttga taatantaga gaaatgaagc acaggaggac 360
tgttgctcag acctcagcag agacacttcc agctgcagag tctcagagag agtggaatga 420
aagataacat antcagagag gagactatca ncttgagcca ntctcagcca gagacacctg 480
acagaatggg tgtgaaggag c 501

<210> 228
<211> 501
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(501)
<223> n = A,T,C or G

<400> 228
gcaggttccc ttttatgggc caggtggtaa ctggaacaca gaacagtgaa ggacagaacc 60
ttggaccaca ggccattcct caggatggca gtataacaca tcagatttct aggcctaatc 120
ctccaaattt tggtccaggc tttgtcaatg attcacagcg taagcagtat gaagagtggc 180
tccaggagac ccaacagctg cttcaaatgc agcagaagta tcttgaagaa caaattggtg 240
ctcacagaaa atctaagaag gccctttcag ctaaacaacg tactgccaag aaagctgggc 300
gtgaatttcc agaggaagat gcagaacaac tcaagcatgt tactgaacag caaagcatgg 360
ttcagaaaca gctagaacag attcgtaaac aacagaaaga acatgctgaa ttgattgaag 420
attatcggat caaacagcag cancaatgng caatggcccc acctaccatg atgcccagng 480
tccagcccca ncccccctaa t 501

<210> 229
<211> 4099
<212> DNA
<213> Homo sapiens

<400> 229
cagctgccag ccgaggaggc gcggcggaga ggggactgcg gtcagctgcg tccacttggg 60
gctgtgcggc ggtcccgcgc ccggcgatgt tcccgggcac tccctgagta gcggcagctt 120
atcccccgcc cgctagcccg ccctggtccc cggctcgctc gctggctggc gcggccccgg 180
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ggaacgaggg ggacacattc caccaggaca accggccgtc ggggcttatc cgcacttacc 420
tggggagaag ccctctggtc tccggggacg agagcagctt gttgctgaac gcggccagca 480
cggtcgcgcg tccggtgttc accgagtatc aggccagtgc gtttgggaat gtcaagctgg 540
tggtccacga ctgtcccgtc tgggacatat ttgacagtga ttggtacact tctcgaaatc 600
taattggggg cgctgacatc attgtgatca aatacaacgt taatgacaag ttttcattcc 660
atgaagtaaa ggataattat attccagtga taaaaagagc attaaattca gttccagtaa 720
ttattgctgc tgttggtacc agacaaaatg aagagttacc ttgtacatgc ccactatgta 780
cctcagacag agggagctgt gttagtacaa ctgaagggat ccaacttgca aaagaactag 840
gagcaaccta tcttgaactc cacagccttg atgacttcta cataggaaag tattttggag 900
gagtgttgga gtattttatg attcaagcct taaatcagaa gacaagtgaa aaaatgaaga 960
aaagaaaaat gagcaactcc tttcatggaa ttagaccacc tcaacttgaa caaccagaaa 1020
aaatgcctgt cttaaaggct gaagcgtcac attataactc tgacttaaat aacttgctgt 1080
tctgctgcca gtgtgtggac gtggtatttt ataaccccga tttaaagaaa gttgtagagg 1140
cccacaagat cgttctctgc gctgtaagcc atgttttcat gctgcttttc aatgtgaaga 1200

gtcccactga cattcaggat tccagtatca tccgaactac ccaggatctt tttgctataa 1260
acagagatac tgcatttcca ggtgctagcc atgaatcttc aggcaaccca ccattacgag 1320
tcattgttaa agacgccctc ttctgttctt gtttatcaga catccttcgc ttcatttatt 1380
caggtgcttt tcagtgggaa gaattggaag aagatatcag gaagaagttg aaagattctg 1440
gggatgtttc aaatgtaatc gagaaagtta aatgcatttt aaaaacacca ggaaagatta 1500
attgcctaag gaattgcaaa acctatcaag ccagaaaacc tttgtggttt tataacactt 1560
ccctcaagtt tttccttaat aagccgatgc ttgccgatgt tgtcttcgaa attcaaggta 1620
cgacagtgcc agcccacagg gccatcctgg tggcccgttg tgaagtgatg gcagccatgt 1680
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tccaggccat gtgtctcctg atctgtgccg agatgtacca agtgtccaga ctgcagcaca 1860
tctgtgagct gttcatcatt acccagctgc agagcatgcc aagcagggaa ctggcatcca 1920
tgaaccttga tatagttgac ctgcttaaaa aggccaagtt tcaccactct gattgccttt 1980
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tgtacttgaa gcagcttgcg gaatacagga agtatattca ctcccggaaa tgtcgttgct 2160
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cagttaagaa atgcttagat taaaaaaaaa aaattacgta ggattaatac agaaatttaa 2520
tcatgtctga ttaattgctc tattaaaata aggggcattt aaagacccag cataaccatt 2580
tgtataatga gaaatctagg ggaaaaccaa tcagtccaac atgagatttt aggaatagaa 2640
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atcatcataa aaaaaatacc tgcttttcat ctggacaacc caattgagcc actttatctc 2760
cttttggcaa tctgagtagg cggggaacct aggcagggct ggctttctta gcgtgtaact 2820
tgtgtagcag cacagggccc acacttagaa ggaccccaca cttggttcaa ggctctgcta 2880
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ctcaaaatta tgtctgtttc gtggtgggaa atatcctatg ttttcttgct caaacacctt 3000
tctctctgaa agcagaaaaa ggcactgata taaagggaag agaaggaggc tcaccggagg 3060
gaagagaaca tagtgaagat tcccgccttt ggggaggtct ggaccaccca gggcctccac 3120
tgccaccttg gctggcaagg gagaaatgtg ttgtgttgtc ttagctttaa aacagtcaca 3180
gttcttgctc tatcatagat gaacaaatac tttcttgatc attctgtaag accaggaggt 3240
tggtaagagt gactaaccag cctaacttta atacacatgt ataaagatgt tcacagagaa 3300
agatgctctg tagagaattt gctaccgaag ttggctcaag aatttgtttt tagtgttatt 3360
taccaagatt aggacgtcag tggcttaaat tctttgaatt cttttcaagg actgcaagat 3420
tatttgataa agagtagcat gaatcttgtg ctctaatatt acacagtaag ttcaaagaaa 3480
ggatgtaagt caaagacttg ttacatagag ggaaaatgga ctgggataga ggacagactg 3540
atagtttctt tctttcatat cacatgtata gagaaataat tatatcagaa actcacaaac 3600
ctagacatgg aaaaacagat tactgtctat tgtcagcatc attttcatct gtaagtcact 3660
actggaatat atttttcttt taatttccag tgactttaga atacacacag tttttccgac 3720
ttttcaaaaa tttgattaaa tggttttata gtataatatt gggaccccat accgttagcc 3780
cttgtatgta taccaacact gccaaagtaa aacattaggt caggcatggt ggctcaggcc 3840
tgtaatccca gcattttggg aggctgaggc aagtggataa cttgaggtca tgagttcgaa 3900
accagcctgg ccaaaacagt gaaaccccgt ctctactaaa aatacaaaat tagccagatg 3960
tggtggcgca cacctgtaat cccagctact caggaagctg aggcaggaaa atcgcttgaa 4020
cctgggaggt ggaagttgca gtgagccgag atcgcaccac tgcactccag cctgggtgac 4080
aagagcgaaa ctccatctc 4099

<210> 230
<211> 2649
<212> DNA
<213> Homo sapiens

<400> 230
gagagagaga gagagagaga ggagcgagag agtgtgagcg agaaagaata aaaggaaaga 60
agattttctc tatgtatata aagatggcca cgttagcaaa cggacaggct gacaacgcaa 120
gcctcagtac caacgggctc ggcagcagcc cgggcagtgc cgggcacatg aacggattaa 180

gccacagccc ggggaacccg tcgaccattc ccatgaagga ccacgatgcc atcaagctgt 240
tcattgggca gatcccccgc aacctggatg agaaggacct caagcccctc ttcgaggagt 300
ttggcaaaat ctacgagctt acggttctga aggacaggtt cacaggcatg cacaaaggct 360
gcgccttcct cacctactgc gagcgtgagt cagcgctgaa ggcccagagc gcgctgcacg 420
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Pro Met Leu Ala Asp Val Val Phe Glu Ile Gln Gly Thr Thr Val Pro
            420                 425                 430
Ala His Arg Ala Ile Leu Val Ala Arg Cys Glu Val Met Ala Ala Met
        435                 440                 445
Phe Asn Gly Asn Tyr Met Glu Ala Lys Ser Val Leu Ile Pro Val Tyr
    450                 455                 460
Gly Val Ser Lys Glu Thr Phe Leu Ser Phe Leu Glu Tyr Leu Tyr Thr
465                 470                 475                 480
Asp Ser Cys Cys Pro Ala Gly Ile Phe Gln Ala Met Cys Leu Leu Ile
                485                 490                 495
```

```
Cys Ala Glu Met Tyr Gln Val Ser Arg Leu Gln His Ile Cys Glu Leu
            500                 505                 510
Phe Ile Ile Thr Gln Leu Gln Ser Met Pro Ser Arg Glu Leu Ala Ser
        515                 520                 525
Met Asn Leu Asp Ile Val Asp Leu Leu Lys Lys Ala Lys Phe His His
    530                 535                 540
Ser Asp Cys Leu Ser Thr Trp Leu Leu His Phe Ile Ala Thr Asn Tyr
545                 550                 555                 560
Leu Ile Phe Ser Gln Lys Pro Glu Phe Gln Asp Leu Ser Val Glu Glu
                565                 570                 575
Arg Ser Phe Val Glu Lys His Arg Trp Pro Ser Asn Met Tyr Leu Lys
            580                 585                 590
Gln Leu Ala Glu Tyr Arg Lys Tyr Ile His Ser Arg Lys Cys Arg Cys
        595                 600                 605
Leu Val Met
    610
```

<210> 234
<211> 494
<212> PRT
<213> Homo sapiens

<400> 234

```
Met Tyr Ile Lys Met Ala Thr Leu Ala Asn Gly Gln Ala Asp Asn Ala
                5                   10                  15
Ser Leu Ser Thr Asn Gly Leu Gly Ser Ser Pro Gly Ser Ala Gly His
            20                  25                  30
Met Asn Gly Leu Ser His Ser Pro Gly Asn Pro Ser Thr Ile Pro Met
        35                  40                  45
Lys Asp His Asp Ala Ile Lys Leu Phe Ile Gly Gln Ile Pro Arg Asn
    50                  55                  60
Leu Asp Glu Lys Asp Leu Lys Pro Leu Phe Glu Glu Phe Gly Lys Ile
65                  70                  75                  80
Tyr Glu Leu Thr Val Leu Lys Asp Arg Phe Thr Gly Met His Lys Gly
                85                  90                  95
Cys Ala Phe Leu Thr Tyr Cys Glu Arg Glu Ser Ala Leu Lys Ala Gln
            100                 105                 110
Ser Ala Leu His Glu Gln Lys Thr Leu Pro Gly Met Asn Arg Pro Ile
        115                 120                 125
Gln Val Lys Pro Ala Asp Ser Glu Ser Arg Gly Asp Arg Lys Leu Phe
    130                 135                 140
Val Gly Met Leu Asn Lys Gln Gln Ser Glu Asp Asp Val Arg Arg Leu
145                 150                 155                 160
Phe Glu Ala Phe Gly Asn Ile Glu Glu Cys Thr Ile Leu Arg Gly Pro
                165                 170                 175
Asp Gly Asn Ser Lys Gly Cys Ala Phe Val Lys Tyr Ser Ser His Ala
            180                 185                 190
Glu Ala Gln Ala Ala Ile Asn Ala Leu His Gly Ser Gln Thr Met Pro
        195                 200                 205
Gly Ala Ser Ser Ser Leu Val Val Lys Phe Ala Asp Thr Asp Lys Glu
    210                 215                 220
Arg Thr Met Arg Arg Met Gln Gln Met Ala Gly Gln Met Gly Met Phe
225                 230                 235                 240
Asn Pro Met Ala Ile Pro Phe Gly Ala Tyr Gly Ala Tyr Ala Gln Ala
                245                 250                 255
Leu Met Gln Gln Gln Ala Ala Leu Met Ala Ser Val Ala Gln Gly Gly
            260                 265                 270
Tyr Leu Asn Pro Met Ala Ala Phe Ala Ala Ala Gln Met Gln Gln Met
```

```
        275                 280                 285
Ala Ala Leu Asn Met Asn Gly Leu Ala Ala Ala Pro Met Thr Pro Thr
    290                 295                 300
Ser Gly Gly Ser Thr Pro Pro Gly Ile Thr Ala Pro Ala Val Pro Ser
305                 310                 315                 320
Ile Pro Ser Pro Ile Gly Val Asn Gly Phe Thr Gly Leu Pro Pro Gln
                325                 330                 335
Ala Asn Gly Gln Pro Ala Ala Glu Ala Val Phe Ala Asn Gly Ile His
            340                 345                 350
Pro Tyr Pro Ala Gln Ser Pro Thr Ala Ala Asp Pro Leu Gln Gln Ala
        355                 360                 365
Tyr Ala Gly Val Gln Gln Tyr Ala Gly Pro Ala Tyr Pro Ala Ala Tyr
    370                 375                 380
Gly Gln Ile Ser Gln Ala Phe Pro Gln Pro Pro Pro Met Ile Pro Gln
385                 390                 395                 400
Gln Gln Arg Glu Gly Pro Glu Gly Cys Asn Leu Phe Ile Tyr His Leu
                405                 410                 415
Pro Gln Glu Phe Gly Asp Ala Glu Leu Met Gln Met Phe Leu Pro Phe
            420                 425                 430
Gly Asn Val Ile Ser Ser Lys Val Phe Val Asp Arg Ala Thr Asn Gln
        435                 440                 445
Ser Lys Cys Phe Gly Phe Val Ser Phe Asp Asn Pro Ala Ser Ala Gln
    450                 455                 460
Thr Ala Ile Gln Ala Met Asn Gly Phe Gln Ile Gly Met Lys Arg Leu
465                 470                 475                 480
Lys Val Gln Leu Lys Arg Pro Lys Asp Ala Asn Arg Pro Tyr
                485                 490
```

<210> 235
<211> 826
<212> PRT
<213> Homo sapiens

<400> 235

```
Met Glu Gly Ala Gly Gly Ala Asn Asp Lys Lys Lys Ile Ser Ser Glu
                  5                  10                  15
Arg Arg Lys Glu Lys Ser Arg Asp Ala Ala Arg Ser Arg Arg Ser Lys
             20                  25                  30
Glu Ser Glu Val Phe Tyr Glu Leu Ala His Gln Leu Pro Leu Pro His
         35                  40                  45
Asn Val Ser Ser His Leu Asp Lys Ala Ser Val Met Arg Leu Thr Ile
     50                  55                  60
Ser Tyr Leu Arg Val Arg Lys Leu Leu Asp Ala Gly Asp Leu Asp Ile
 65                  70                  75                  80
Glu Asp Asp Met Lys Ala Gln Met Asn Cys Phe Tyr Leu Lys Ala Leu
                 85                  90                  95
Asp Gly Phe Val Met Val Leu Thr Asp Asp Gly Asp Met Ile Tyr Ile
            100                 105                 110
Ser Asp Asn Val Asn Lys Tyr Met Gly Leu Thr Gln Phe Glu Leu Thr
        115                 120                 125
Gly His Ser Val Phe Asp Phe Thr His Pro Cys Asp His Glu Glu Met
    130                 135                 140
Arg Glu Met Leu Thr His Arg Asn Gly Leu Val Lys Lys Gly Lys Glu
145                 150                 155                 160
Gln Asn Thr Gln Arg Ser Phe Phe Leu Arg Met Lys Cys Thr Leu Thr
                165                 170                 175
Ser Arg Gly Arg Thr Met Asn Ile Lys Ser Ala Thr Trp Lys Val Leu
            180                 185                 190
```

```
His Cys Thr Gly His Ile His Val Tyr Asp Thr Asn Ser Asn Gln Pro
        195                 200                 205
Gln Cys Gly Tyr Lys Lys Pro Pro Met Thr Cys Leu Val Leu Ile Cys
    210                 215                 220
Glu Pro Ile Pro His Pro Ser Asn Ile Glu Ile Pro Leu Asp Ser Lys
225                 230                 235                 240
Thr Phe Leu Ser Arg His Ser Leu Asp Met Lys Phe Ser Tyr Cys Asp
                245                 250                 255
Glu Arg Ile Thr Glu Leu Met Gly Tyr Glu Pro Glu Glu Leu Leu Gly
            260                 265                 270
Arg Ser Ile Tyr Glu Tyr Tyr His Ala Leu Asp Ser Asp His Leu Thr
        275                 280                 285
Lys Thr His His Asp Met Phe Thr Lys Gly Gln Val Thr Thr Gly Gln
    290                 295                 300
Tyr Arg Met Leu Ala Lys Arg Gly Gly Tyr Val Trp Val Glu Thr Gln
305                 310                 315                 320
Ala Thr Val Ile Tyr Asn Thr Lys Asn Ser Gln Pro Gln Cys Ile Val
                325                 330                 335
Cys Val Asn Tyr Val Val Ser Gly Ile Ile Gln His Asp Leu Ile Phe
            340                 345                 350
Ser Leu Gln Gln Thr Glu Cys Val Leu Lys Pro Val Glu Ser Ser Asp
        355                 360                 365
Met Lys Met Thr Gln Leu Phe Thr Lys Val Glu Ser Glu Asp Thr Ser
    370                 375                 380
Ser Leu Phe Asp Lys Leu Lys Lys Glu Pro Asp Ala Leu Thr Leu Leu
385                 390                 395                 400
Ala Pro Ala Ala Gly Asp Thr Ile Ile Ser Leu Asp Phe Gly Ser Asn
                405                 410                 415
Asp Thr Glu Thr Asp Asp Gln Gln Leu Glu Glu Val Pro Leu Tyr Asn
            420                 425                 430
Asp Val Met Leu Pro Ser Pro Asn Glu Lys Leu Gln Asn Ile Asn Leu
        435                 440                 445
Ala Met Ser Pro Leu Pro Thr Ala Glu Thr Pro Lys Pro Leu Arg Ser
    450                 455                 460
Ser Ala Asp Pro Ala Leu Asn Gln Glu Val Ala Leu Lys Leu Glu Pro
465                 470                 475                 480
Asn Pro Glu Ser Leu Glu Leu Ser Phe Thr Met Pro Gln Ile Gln Asp
                485                 490                 495
Gln Thr Pro Ser Pro Ser Asp Gly Ser Thr Arg Gln Ser Ser Pro Glu
            500                 505                 510
Pro Asn Ser Pro Ser Glu Tyr Cys Phe Tyr Val Asp Ser Asp Met Val
        515                 520                 525
Asn Glu Phe Lys Leu Glu Leu Val Glu Lys Leu Phe Ala Glu Asp Thr
    530                 535                 540
Glu Ala Lys Asn Pro Phe Ser Thr Gln Asp Thr Asp Leu Asp Leu Glu
545                 550                 555                 560
Met Leu Ala Pro Tyr Ile Pro Met Asp Asp Asp Phe Gln Leu Arg Ser
                565                 570                 575
Phe Asp Gln Leu Ser Pro Leu Glu Ser Ser Ser Ala Ser Pro Glu Ser
            580                 585                 590
Ala Ser Pro Gln Ser Thr Val Thr Val Phe Gln Gln Thr Gln Ile Gln
        595                 600                 605
Glu Pro Thr Ala Asn Ala Thr Thr Thr Thr Ala Thr Thr Asp Glu Leu
    610                 615                 620
Lys Thr Val Thr Lys Asp Arg Met Glu Asp Ile Lys Ile Leu Ile Ala
625                 630                 635                 640
Ser Pro Ser Pro Thr His Ile His Lys Glu Thr Thr Ser Ala Thr Ser
                645                 650                 655
Ser Pro Tyr Arg Asp Thr Gln Ser Arg Thr Ala Ser Pro Asn Arg Ala
```

```
            660                 665                 670
Gly Lys Gly Val Ile Glu Gln Thr Glu Lys Ser His Pro Arg Ser Pro
        675                 680                 685
Asn Val Leu Ser Val Ala Leu Ser Gln Arg Thr Thr Val Pro Glu Glu
    690                 695                 700
Glu Leu Asn Pro Lys Ile Leu Ala Leu Gln Asn Ala Gln Arg Lys Arg
705                 710                 715                 720
Lys Met Glu His Asp Gly Ser Leu Phe Gln Ala Val Gly Ile Gly Thr
                725                 730                 735
Leu Leu Gln Gln Pro Asp Asp His Ala Ala Thr Thr Ser Leu Ser Trp
            740                 745                 750
Lys Arg Val Lys Gly Cys Lys Ser Ser Glu Gln Asn Gly Met Glu Gln
        755                 760                 765
Lys Thr Ile Ile Leu Ile Pro Ser Asp Leu Ala Cys Arg Leu Leu Gly
    770                 775                 780
Gln Ser Met Asp Glu Ser Gly Leu Pro Gln Leu Thr Ser Tyr Asp Cys
785                 790                 795                 800
Glu Val Asn Ala Pro Ile Gln Gly Ser Arg Asn Leu Leu Gln Gly Glu
                805                 810                 815
Glu Leu Leu Arg Ala Leu Asp Gln Val Asn
            820                 825
```

<210> 236
<211> 342
<212> PRT
<213> Homo sapiens

<400> 236

```
Asn Asn Asn Asn Ser Lys His Thr Gly His Lys Ser Ala Cys Val Pro
                  5                  10                  15
Asn Met Thr Glu Arg Arg Arg Asp Glu Leu Ser Glu Glu Ile Asn Asn
             20                  25                  30
Leu Arg Glu Lys Val Met Lys Gln Ser Glu Glu Asn Asn Asn Leu Gln
         35                  40                  45
Ser Gln Val Gln Lys Leu Thr Glu Glu Asn Thr Thr Leu Arg Glu Gln
     50                  55                  60
Val Glu Pro Thr Pro Glu Asp Glu Asp Asp Asp Ile Glu Leu Arg Gly
 65                  70                  75                  80
Ala Ala Ala Ala Ala Ala Pro Pro Pro Pro Ile Glu Glu Glu Cys Pro
                 85                  90                  95
Glu Asp Leu Pro Glu Lys Phe Asp Gly Asn Pro Asp Met Leu Ala Pro
            100                 105                 110
Phe Met Ala Gln Cys Gln Ile Phe Met Glu Lys Ser Thr Arg Asp Phe
        115                 120                 125
Ser Val Asp Arg Val Arg Val Cys Phe Val Thr Ser Met Met Thr Gly
    130                 135                 140
Arg Ala Ala Arg Trp Ala Ser Ala Lys Leu Glu Arg Ser His Tyr Leu
145                 150                 155                 160
Met His Asn Tyr Pro Ala Phe Met Met Glu Met Lys His Val Phe Glu
                165                 170                 175
Asp Pro Gln Arg Arg Glu Val Ala Lys Arg Lys Ile Arg Arg Leu Arg
            180                 185                 190
Gln Gly Met Gly Ser Val Ile Asp Tyr Ser Asn Ala Phe Gln Met Ile
        195                 200                 205
Ala Gln Asp Leu Asp Trp Asn Glu Pro Ala Leu Ile Asp Gln Tyr His
    210                 215                 220
Glu Gly Leu Ser Asp His Ile Gln Glu Glu Leu Ser His Leu Glu Val
225                 230                 235                 240
```

```
Ala Lys Ser Leu Ser Ala Leu Ile Gly Gln Cys Ile His Ile Glu Arg
                245                 250                 255
Arg Leu Ala Arg Ala Ala Ala Ala Arg Lys Pro Arg Ser Pro Pro Arg
            260                 265                 270
Ala Leu Val Leu Pro His Ile Ala Ser His His Gln Val Asp Pro Thr
        275                 280                 285
Glu Pro Val Gly Gly Ala Arg Met Arg Leu Thr Gln Glu Glu Lys Glu
    290                 295                 300
Arg Arg Arg Lys Leu Asn Leu Cys Leu Tyr Cys Gly Thr Gly Gly His
305                 310                 315                 320
Tyr Ala Asp Asn Cys Pro Ala Lys Ala Ser Lys Ser Ser Pro Ala Gly
                325                 330                 335
Asn Ser Pro Ala Pro Leu
            340
```

<210> 237
<211> 403
<212> DNA
<213> Homo sapiens

<400> 237
ccagtgtggt ggaattccag cctcgtgccg ggagtcgccg cattgtggtc cgcttctctg 60
cactatgtcg ggtggcctcc tgaaggcgct gcgcagcgac tcctacgtgg agctgagcca 120
gtaccgggac cagcacttcc ggggtgacaa tgaagaacaa gaaaaattac tgaagaaaag 180
ctgtacgtta tatgttggaa atctttcttt ttacacaact gaagaacaaa tctatgaact 240
cttcagcaaa agtggtgaca taaagaaaat cattatgggt ctggataaaa tgaagaaaac 300
agcatgtgga ttctgttttg tggaatatta ctcacgcgca gatgcggaaa acgccatgcg 360
gtacataaat gggacgcgtc tggatgaccg aatcattcgc aca 403

<210> 238
<211> 183
<212> DNA
<213> Homo sapiens

<400> 238
tattaatagt aatcaattac ggggtcatta gttcatagcc catatatgga gttccgcgtt 60
acataactta cggtaaatgg cccgcctggc tgaccgccca acgacccccg cccattgacg 120
tcaataatga cgtatgttcc catagtaacg ccaataggga ctttccattg acgtcaatgg 180
gtg 183

<210> 239
<211> 403
<212> DNA
<213> Homo sapiens

<400> 239
ttttgatgct ttctttcatg ggaatagtca ctttttttatt tagtaaatcg cattgctgga 60
accaccaagg agtgtggaat gtccttgagt gtattattta tgcaagtcac agtcacgttg 120
ccatcatggc agctatgtga aacactaata aatgtgtttt tacttttttat tcccgttaaa 180
actgatgtaa aacaggataa aggcttgtta tagtcactta taagtatctg ggtctaagta 240
atttccttag atgtttctaa agaaacattt tcagctttgc tcccattatg attccaataa 300
ggaacgcttt cctagtgcaa ttttaggagt aaagtttgaa gagataaaaa tagccaaaga 360
taggagacgt ctgaattttg aatgataaac agtgatgttt taa 403

<210> 240
<211> 3148
<212> DNA
<213> Homo sapiens

<400> 240
aacttctcgg gaagatgagg cagtttggca tctgtggccg agttgctgtt gccgggtgat 60
agttggagcg gagacttagc ataatggcag aacctgtttc tccactgaag cactttgtgc 120
tggctaagaa ggcgattact gcagtctttg accagttact ggagtttgtt actgaaggat 180
cacattttgt tgaagcaaca tataagaatc cggaacttga tcgaatagcc actgaagatg 240
atctggtaga aatgcaagga tataaagaca agctttccat cattggtgag gtgctatctc 300
ggagacacat gaaggtggca ttttttggca ggacaagcag tgggaagagc tctgttatca 360
atgcaatgtt gtgggataaa gttctcccta gtgggattgg ccatataacc aattgcttcc 420
taagtgttga aggaactgat ggagataaag cctatcttat gacagaagga tcagatgaaa 480
aaaagagtgt gaagacagtt aatcaactgg cccatgccct tcacatggac aaagatttga 540
aagctggctg tcttgtacgt gtgttttggc caaaagcaaa atgtgccctc ttgagagatg 600
acctggtgtt agtagacagt ccaggcacag atgtcactac agagctggat agctggattg 660
ataagttttg cctagatgct gatgtctttg ttttggtcgc aaactctgaa tcaacactaa 720
tgaatacgga aaaacacttt tttcacaagg tgaatgagcg gctttccaag cctaatattt 780
tcattctcaa taatcgttgg gatgcctctg catcagagcc agaatatatg gaagacgtac 840
gcagacagca catggaaaga tgcctgcatt tcttggtgga ggagctcaaa gttgtaaatg 900
ctttagaagc acagaatcgt atcttctttg tttcagcaaa ggaagttctt agtgctagaa 960
agcaaaaagc acaggggatg ccagaaagtg gtgtggcact tgctgaagga tttcatgcaa 1020
gattacagga atttcagaat tttgaacaaa tctttgagga gtgtatctcg cagtcagcag 1080
tgaaaacaaa gttcgaacag cacactatca gagctaaaca gatactagct actgtgaaaa 1140
acataatgga ttcagtaaac ctggcagctg aagataaaag gtttcatgtg caatgacaga 1200
tgaaatttgt cgactgtctg ttttggttga tgaattttgt tcagagtttc atcctaatcc 1260
agatgtatta aaaatatata aaagtgaatt aaataagcac atagaggatg gtatgggaag 1320
aaatttggct gatcgatgca ccgatgaagt aaacgcctta gtgcttcaga cccagcaaga 1380
aattattgaa aatttgaagc cattacttcc agctggtata caggataaac tacatacact 1440
gatcccttgc aagaaatttg atctcagtta taatctaaat taccacaagt tatgttcaga 1500
ttttcaagag gatattgtat ttcgtttttc cctgggctgg tcttcccttg tacatcgatt 1560
tttgggccct agaaatgctc aaagggtgct cctaggatta tcagagccta tctttcagct 1620
ccctagatct ttagcttcta ctcccactgc tcctaccact ccagcaacgc cagataatgc 1680
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atctgtttca ttaactatgt atggagcttt gtatctttat gaaagactga gctggaccac 1860
ccatgccaag gagcgagcct ttaaacagca gtttgtaaac tatgcaactg aaaaactgag 1920
gatgattgtt agctccacga gtgcaaactg cagtcaccaa gtaaaacaac aaatagctac 1980
cacttttgct cgcctgtgcc aacaagttga tattactcaa aaacagctgg aagaagaaat 2040
tgctagatta cccaaagaaa tagatcagtt ggagaaaata caaaacaatt caaagctctt 2100
aagaaataaa gctgttcaac ttgaaaatga gctggagaat tttactaagc agtttctacc 2160
ttcaagcaat gaagaatcct aacaatagag attgctttgg tgaccatgat aggaggaaac 2220
gaaacttgta agattggaac agttgttatt tttatgaaat tactttaaat atgaattgta 2280
ctaactgtac ctaaatagca aagccctgtg tagattctgg taatgatctg tctcagggta 2340
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atcatgaatt agttacaagc aacagtacca acttatgtga cccctgaggg gtggggctgt 2460
gagctcttaa tttgtttttg attctgaaaa actctgcttc ctggcatcca ggagttagag 2520
attgagcctt tcatcttctt tctcaaaact agttttgat gctttctttc atgggaatag 2580
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agtgtattat ttatgcaagt cacagtcacg ttgccatcat ggcagctatg tgaaacacta 2700
ataaatgtgt ttttactttt tattcccgtt aaaactgatg taaaacagga taaaggcttg 2760
ttatagtcac ttataagtat ctgggtctaa gtaatttcct tagatgtttc taaagaaaca 2820
ttttcagctt tgctcccatt atgattccaa taaggaacgc tttcctagtg caattttagg 2880
agtaaagttt gaagagataa aaatagccaa agataggaga cgtctgaatt ttgaatgata 2940
aacagtgatg ttttaaaaaa gctgttgttc ttcaggaggc atttgcctag gatattgctg 3000
gattataccc cattggaggc ttttaatttt atttgtatga attttccagg atttcattaa 3060
aaattattat tgtatttttt accttaatga aagattttgg gttcaaatat ctttctatat 3120
taaaagctga ttgagtctgt acatatgt 3148

<210> 241
<211> 283
<212> DNA

<213> Homo sapiens

<400> 241
ttatttttcc cctcaaattc atgattttta cgtctgttac aaagggaatt ttgctgatag 60
ctctttgggt cccactgttc cattttatgc taatagattc cattctaggg cccagccgtc 120
tcttgactga tggtgttccc tttaaccctt ggcatgtata atagaatttt ggtgaatgaa 180
agaacccaaa taggccagat agtcccccca ggccctgata tccataaaag gcttgggaat 240
gcattatgta attgtcctta gtctttttgt tgttttagaa aaa 283

<210> 242
<211> 5526
<212> DNA
<213> Homo sapiens

<400> 242
cgggccctgg ggctcgggag tcgggggcgg tgggacagtg cggctactct tgatcctctc 60
cggctgcttg gtctacggca cagctgaaac tgatgtaaat gtggtcatgc ttcaggaatc 120
ccaagtttgt gaaaagcgtg ccagccaaca attctgttac acaaatgtgc ttatcccaaa 180
atggcatgat atatggacac ggatacagat ccgagtaaat agttccagat tggttcgagt 240
cacccaggtg gagaatgagg agaaactgaa ggagctagag cagtttagta tctggaactt 300
tttttcctcc tttttaaaag agaaattgaa tgacacctat gttaacgtgg gtctatacag 360
cacaaaaacc tgcctcaaag ttgagattat agagaaggac accaagtaca gtgtcattgt 420
gatccggaga tttgatccca aactctttct tgttttcctt cttggactta tgctattttt 480
ttgtggagac ttgctgagca gaagtcaaat tttctactac tctactggga tgactgtggg 540
aattgtggcc tctctgctaa tcatcatttt tatactatct aagtttatgc ctaagaaaag 600
tcccatttac gtcatcctgg tgggaggctg gtctttttct ctgtacctca ttcaactagt 660
ttttaaaaat ttacaagaga tctggaggtg ttactggcag tatcttttaa gttatgtcct 720
cacagttgga ttcatgagtt ttgcagtatg ttacaagtat gggcccttgg agaatgaacg 780
aagtatcaac ctgctgacct ggaccttgca gctgatgggc ctgtgtttca tgtattctgg 840
catccagata ccacatattg cccttgccat tatcatcatt gctctttgta ctaagaacct 900
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ccgaaaggct ttagaggagc tccgagaatt ttgtaacagt ccagactgct ctgcttggaa 1080
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cctcacgcca aatgaagttt ctgtccatga gcaggagtat ggattaggga gcattattgc 1200
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tgctatcaca cagaacaact ttctaaccta ggtagtggtc agttatcttt acgtggactg 1320
gcttggtgcc ttggtccatg ttgcatgtgt tgtgcaattg ctttcaaccc tttgaaacag 1380
agtgagatag atagggtaga aattctccta ctgaaataag aggcctaaaa aggcctccct 1440
ttggaaatgg gaggtctcta tgggatccct gaggaaggag agtggataaa gtagtgaatg 1500
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aaccagcaag tgctccagag tgacacaccc cctaggcccc tacatattta ttaatatgga 1920
ttatccatta aagccccagg agctgttgtt ttaagctttg atttagttct catacatatg 1980
atagaaagtc ctatttgcct ttaggaacat gcctgtaggc tcttctgcag gtgagatgta 2040
ctgggctttt tattatattc aactttcaat tccatcttaa aaaacatttg tattcttctc 2100
ttcccattct tccttaccct gcctttgccc tttcaggaag ggtcagttcc cttacctgtg 2160
aactatgtat gttcagagta gcattattcc tgctagctag gagaagtcat cttgtttagg 2220
ggatttggat gcttttata cgttctccat tttcctgtca ttgggtcatg ttatctttga 2280
gttgctatga aatcaggaaa ctgtctcctt ttcctttccc ttcctttgtc tacatgctct 2340
gtccattcct ttcagccttt tctcaccacc catactcccc caaatctggg taatttttaa 2400
gccttgaaac tatgtagttt cttgatacac aatttgtagt tatgcagcag ccacaatttg 2460
cattgccagg aaataggctc caggttatct tcatgcctct gggtgctcat tcagctgtca 2520
agtttccatg aacttacact tatttatgat tgcgtttctg acctgagatg tatgctgcct 2580
gttattgcag tagcattagt ttcagattct tttgccattg caaagtaccc cttataaacc 2640

agcaatgtca tctgtgagga agcaaattct caagtgtctg tcatttactt ggttcttttt 2700
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<210> 243
<211> 303
<212> DNA
<213> Homo sapiens

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agctcaccgc atgcccttct tggaggccgc gggccacaag cttggcgcca agaaggaggg 240
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ggc 303

<210> 244
<211> 2393
<212> DNA
<213> Homo sapiens

<400> 244
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<210> 245
<211> 473
<212> DNA
<213> Homo sapiens

<400> 245
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ctgcatcctt tacattagcc actaaatacg ttattgcttg atgaagacct ttcacagaat 180
cctatggatt gcagcatttc acttggctac ttcataccca tgccttaaag aggggcagtt 240
tctcaaaagc agaaacatgc cgccagttct caagttttcc tcctaactcc atttgaatgt 300
aagggcagct ggccccccaat gtggggaggt ccgaacattt tctgaattcc cattttcttg 360
ttcgcggcta aatgacagtt tctgtcatta cttagattcc gatctttccc aaaggtgttg 420
atttacaaag aggccagcta atagcagaaa tcatgaccct gaaagagaga tga 473

<210> 246
<211> 513
<212> DNA
<213> Homo sapiens

<400> 246
ggcattaact tttagaattt gggctggtga gattaatttt ttttaatatc ccagctagag 60
atatggcctt taactgacct aaagaggtgt gttgtgattt aatttttcc cgttcctttt 120
tcttcagtaa acccaacaat agtctaacct taaaaattga gttgatgtcc ttataggtca 180
ctacccctaa ataaacctga agcaggtgtt ttctcttgga catactaaaa aatacctaaa 240
aggaagctta gatggtctgt gacacaaaaa attcaattac tgtcatctaa tgccagctgt 300
taaaagtgtg gccactgagc atttgatttt ataggaaaaa atagtatttt tgagaataac 360
atagctgtgc tattgcacat ctgttggagg acatcccaga tttgcttata ctcagtgcct 420
gtgatattga gtttaaggat ttgaggcagg ggtaattatt aaacatattg cttctattct 480
tggaaaaata gaagtgtaaa atgttaataa tac 513

<210> 247
<211> 533
<212> DNA
<213> Homo sapiens

<400> 247
ccagtgtggt ggaattcgcg gtaggctggg accataacac aagcatgact atatgaagga 60
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aagagttgga tgcctttccg aaggttcctg agagctatgt agagacttca gccagtggag 180
gtacagtttc tctaatagca tttacaacta tggctttatt aaccataatg gaattctcag 240
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taagaattaa tatagatatt actgttgcca tgaagtgtca atatgttgga gcggatgtat 360
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ttgatctttc accacagcag aaagagtggc agaggatgct gcagctgatt cagagtaggc 480
tacaagaaga gcattcactt caagatgtga tatttaaaag tgcttttaaa agt 533

<210> 248
<211> 1362
<212> DNA
<213> Homo sapiens

<400> 248
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tttggtaaaa gagttggatg cctttccgaa ggttcctgag agctatgtag agacttcagc 180
cagtggaggt acagtttctc taatagcatt tacaactatg gctttattaa ccataatgga 240
attctcagta tatcaagata catggatgaa gtatgaatac gaagtagaca aggatttttc 300
tagcaaatta agaattaata tagatattac tgttgccatg aagtgtcaat atgttggagc 360
ggatgtattg gatttagcag aaacaatggt tgcatctgca gatggtttag tttatgaacc 420
aacagtattt gatctttcac cacagcagaa agagtggcag aggatgctgc agctgattca 480
gagtaggcta caagaagagc attcacttca agatgtgata tttaaaagtg cttttaaaag 540
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aattcatggc catctatatg tcaataaagt agcagggaat tttcacataa cagtgggcaa 660
ggcaattcca catcctcgtg gtcatgcaca tttgggcagc acttgtcaac catggaatct 720
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taatccttta gatggaactg aaaaaattgc tatagatcac aaccagatgt tccaatattt 840

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acaaataagc agaaaacata cttattttaa aaaaaaaaaa aa 1362

<210> 249
<211> 513
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(513)
<223> n = A,T,C or G

<400> 249
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attcaaggag tacctctctc tagaactgta cgctgtacct gcatcagcat tagtaatcaa 180
cctgttaatc caaggtcttt agaaaaactt gaaattattc ctgcaagcca attttgtcca 240
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gttacactaa aaggtgacca atcatggtca cca 513

<210> 250
<211> 1172
<212> DNA
<213> Homo sapiens

<400> 250
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aagatcaaaa ggttaataaa gtaattataa ct 1172

<210> 251

<211> 483
<212> DNA
<213> Homo sapiens

<400> 251
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gacatataga actttacaaa catatgtcca aggactctaa attgagactc ttccacatgt 120
acaatctcat catcctgaag cctataatga agaaaaagat ctagaaactg agttgtggag 180
ctgactctaa tcaaatgtga tgattggaat tagaccattt ggcctttgaa ctttcatagg 240
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actattcttg tttatatttt agatactgaa aggtgctatg cttctgttat tattccaaga 360
ctggagatag gcagggctaa aaaggtatta ttatttttcc tttaatgatg gtgctaaaat 420
tcttcctata aaattcctta aaaataaaga tggtttaatc actaccattg tgaaaacata 480
act 483

<210> 252
<211> 156
<212> PRT
<213> Homo sapiens

<400> 252
Met Ser Gly Gly Leu Leu Lys Ala Leu Arg Ser Asp Ser Tyr Val Glu
1 5 10 15
Leu Ser Gln Tyr Arg Asp Gln His Phe Arg Gly Asp Asn Glu Glu Gln
20 25 30
Glu Lys Leu Leu Lys Lys Ser Cys Thr Leu Tyr Val Gly Asn Leu Ser
35 40 45
Phe Tyr Thr Thr Glu Glu Gln Ile Tyr Glu Leu Phe Ser Lys Ser Gly
50 55 60
Asp Ile Lys Lys Ile Ile Met Gly Leu Asp Lys Met Lys Lys Thr Ala
65 70 75 80
Cys Gly Phe Cys Phe Val Glu Tyr Tyr Ser Arg Ala Asp Ala Glu Asn
85 90 95
Ala Met Arg Tyr Ile Asn Gly Thr Arg Leu Asp Asp Arg Ile Ile Arg
100 105 110
Thr Asp Trp Asp Ala Gly Phe Lys Glu Gly Arg Gln Tyr Gly Arg Gly
115 120 125
Arg Ser Gly Gly Gln Val Arg Asp Glu Tyr Arg Gln Asp Tyr Asp Ala
130 135 140
Gly Arg Gly Gly Tyr Gly Lys Leu Ala Gln Asn Gln
145 150 155

<210> 253
<211> 370
<212> PRT
<213> Homo sapiens

<400> 253
Met Ala Glu Pro Val Ser Pro Leu Lys His Phe Val Leu Ala Lys Lys
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Ala Ile Thr Ala Val Phe Asp Gln Leu Leu Glu Phe Val Thr Glu Gly
20 25 30
Ser His Phe Val Glu Ala Thr Tyr Lys Asn Pro Glu Leu Asp Arg Ile
35 40 45
Ala Thr Glu Asp Asp Leu Val Glu Met Gln Gly Tyr Lys Asp Lys Leu
50 55 60
Ser Ile Ile Gly Glu Val Leu Ser Arg Arg His Met Lys Val Ala Phe
65 70 75 80

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Phe Gly Arg Thr Ser Ser Gly Lys Ser Ser Val Ile Asn Ala Met Leu
                  85                  90                  95
Trp Asp Lys Val Leu Pro Ser Gly Ile Gly His Ile Thr Asn Cys Phe
             100                 105                 110
Leu Ser Val Glu Gly Thr Asp Gly Asp Lys Ala Tyr Leu Met Thr Glu
         115                 120                 125
Gly Ser Asp Glu Lys Lys Ser Val Lys Thr Val Asn Gln Leu Ala His
     130                 135                 140
Ala Leu His Met Asp Lys Asp Leu Lys Ala Gly Cys Leu Val Arg Val
145                 150                 155                 160
Phe Trp Pro Lys Ala Lys Cys Ala Leu Leu Arg Asp Asp Leu Val Leu
                 165                 170                 175
Val Asp Ser Pro Gly Thr Asp Val Thr Thr Glu Leu Asp Ser Trp Ile
             180                 185                 190
Asp Lys Phe Cys Leu Asp Ala Asp Val Phe Val Leu Val Ala Asn Ser
         195                 200                 205
Glu Ser Thr Leu Met Asn Thr Glu Lys His Phe Phe His Lys Val Asn
     210                 215                 220
Glu Arg Leu Ser Lys Pro Asn Ile Phe Ile Leu Asn Asn Arg Trp Asp
225                 230                 235                 240
Ala Ser Ala Ser Glu Pro Glu Tyr Met Glu Asp Val Arg Arg Gln His
                 245                 250                 255
Met Glu Arg Cys Leu His Phe Leu Val Glu Glu Leu Lys Val Val Asn
             260                 265                 270
Ala Leu Glu Ala Gln Asn Arg Ile Phe Phe Val Ser Ala Lys Glu Val
         275                 280                 285
Leu Ser Ala Arg Lys Gln Lys Ala Gln Gly Met Pro Glu Ser Gly Val
     290                 295                 300
Ala Leu Ala Glu Gly Phe His Ala Arg Leu Gln Glu Phe Gln Asn Phe
305                 310                 315                 320
Glu Gln Ile Phe Glu Glu Cys Ile Ser Gln Ser Ala Val Lys Thr Lys
                 325                 330                 335
Phe Glu Gln His Thr Ile Arg Ala Lys Gln Ile Leu Ala Thr Val Lys
             340                 345                 350
Asn Ile Met Asp Ser Val Asn Leu Ala Ala Glu Asp Lys Arg Phe His
         355                 360                 365
Val Gln
     370
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<210> 254
<211> 429
<212> PRT
<213> Homo sapiens

<400> 254

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Leu Ile Leu Ser Gly Cys Leu Val Tyr Gly Thr Ala Glu Thr Asp Val
             20                  25                  30
Asn Val Val Met Leu Gln Glu Ser Gln Val Cys Glu Lys Arg Ala Ser
         35                  40                  45
Gln Gln Phe Cys Tyr Thr Asn Val Leu Ile Pro Lys Trp His Asp Ile
     50                  55                  60
Trp Thr Arg Ile Gln Ile Arg Val Asn Ser Ser Arg Leu Val Arg Val
 65                  70                  75                  80
Thr Gln Val Glu Asn Glu Glu Lys Leu Lys Glu Leu Glu Gln Phe Ser
                 85                  90                  95
Ile Trp Asn Phe Phe Ser Ser Phe Leu Lys Glu Lys Leu Asn Asp Thr
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            100                 105                 110
Tyr Val Asn Val Gly Leu Tyr Ser Thr Lys Thr Cys Leu Lys Val Glu
        115                 120                 125
Ile Ile Glu Lys Asp Thr Lys Tyr Ser Val Ile Val Ile Arg Arg Phe
    130                 135                 140
Asp Pro Lys Leu Phe Leu Val Phe Leu Leu Gly Leu Met Leu Phe Phe
145                 150                 155                 160
Cys Gly Asp Leu Leu Ser Arg Ser Gln Ile Phe Tyr Tyr Ser Thr Gly
                165                 170                 175
Met Thr Val Gly Ile Val Ala Ser Leu Leu Ile Ile Ile Phe Ile Leu
            180                 185                 190
Ser Lys Phe Met Pro Lys Lys Ser Pro Ile Tyr Val Ile Leu Val Gly
        195                 200                 205
Gly Trp Ser Phe Ser Leu Tyr Leu Ile Gln Leu Val Phe Lys Asn Leu
    210                 215                 220
Gln Glu Ile Trp Arg Cys Tyr Trp Gln Tyr Leu Leu Ser Tyr Val Leu
225                 230                 235                 240
Thr Val Gly Phe Met Ser Phe Ala Val Cys Tyr Lys Tyr Gly Pro Leu
                245                 250                 255
Glu Asn Glu Arg Ser Ile Asn Leu Leu Thr Trp Thr Leu Gln Leu Met
            260                 265                 270
Gly Leu Cys Phe Met Tyr Ser Gly Ile Gln Ile Pro His Ile Ala Leu
        275                 280                 285
Ala Ile Ile Ile Ile Ala Leu Cys Thr Lys Asn Leu Glu His Pro Ile
    290                 295                 300
Gln Trp Leu Tyr Ile Thr Cys Arg Lys Val Cys Lys Gly Ala Glu Lys
305                 310                 315                 320
Pro Val Pro Pro Arg Leu Leu Thr Glu Glu Glu Tyr Arg Ile Gln Gly
                325                 330                 335
Glu Val Glu Thr Arg Lys Ala Leu Glu Glu Leu Arg Glu Phe Cys Asn
            340                 345                 350
Ser Pro Asp Cys Ser Ala Trp Lys Thr Val Ser Arg Ile Gln Ser Pro
        355                 360                 365
Lys Arg Phe Ala Asp Phe Val Glu Gly Ser Ser His Leu Thr Pro Asn
    370                 375                 380
Glu Val Ser Val His Glu Gln Glu Tyr Gly Leu Gly Ser Ile Ile Ala
385                 390                 395                 400
Gln Asp Glu Ile Tyr Glu Glu Ala Ser Ser Glu Glu Glu Asp Ser Tyr
                405                 410                 415
Ser Arg Cys Pro Ala Ile Thr Gln Asn Asn Phe Leu Thr
            420                 425
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<210> 255
<211> 531
<212> PRT
<213> Homo sapiens

<400> 255

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Met Ser Arg Ser Pro Gln Arg Ala Leu Pro Pro Gly Ala Leu Pro Arg
                5                  10                  15
Leu Leu Gln Ala Ala Pro Ala Ala Gln Pro Arg Ala Leu Leu Pro Gln
            20                  25                  30
Trp Pro Arg Arg Pro Gly Arg Arg Trp Pro Ala Ser Pro Leu Gly Met
        35                  40                  45
Lys Val Phe Arg Arg Lys Ala Leu Val Leu Cys Ala Gly Tyr Ala Leu
    50                  55                  60
Leu Leu Val Leu Thr Met Leu Asn Leu Leu Asp Tyr Lys Trp His Lys
65                  70                  75                  80
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Glu Pro Leu Gln Gln Cys Asn Pro Asp Gly Pro Leu Gly Ala Ala Ala
                85                  90                  95
Gly Ala Ala Gly Gly Lys Leu Gly Ala Pro Arg Ala Ala Ser Gly Arg
            100                 105                 110
Ala Ala Pro Cys Ser Cys Pro Phe Gly Pro Pro His Ser Leu Pro Pro
        115                 120                 125
Ser Arg Cys Arg Arg Arg Gly Asp Thr Leu Gln Pro Arg Gln Gly Trp
    130                 135                 140
Arg Gly Leu Arg Pro Leu Gln Ala Met Ala Leu Gly Ala Pro Glu Gly
145                 150                 155                 160
Val Gly Asp Lys Arg His Trp Met Tyr Val Phe Thr Thr Trp Arg Ser
                165                 170                 175
Gly Ser Ser Phe Phe Gly Glu Leu Phe Asn Gln Asn Pro Glu Val Phe
            180                 185                 190
Phe Leu Tyr Glu Pro Val Trp His Val Trp Gln Lys Leu Tyr Pro Gly
        195                 200                 205
Asp Ala Val Ser Leu Gln Gly Ala Ala Arg Asp Met Leu Ser Ala Leu
    210                 215                 220
Tyr Arg Cys Asp Leu Ser Val Phe Gln Leu Tyr Ser Pro Ala Gly Ser
225                 230                 235                 240
Gly Gly Arg Asn Leu Thr Thr Leu Gly Ile Phe Gly Ala Ala Thr Asn
                245                 250                 255
Lys Val Val Cys Ser Ser Pro Leu Cys Pro Ala Tyr Arg Lys Glu Val
            260                 265                 270
Val Gly Leu Val Asp Asp Arg Val Cys Lys Lys Cys Pro Pro Gln Arg
        275                 280                 285
Leu Ala Arg Phe Glu Glu Glu Cys Arg Lys Tyr Arg Thr Leu Val Ile
    290                 295                 300
Lys Gly Val Arg Val Phe Asp Val Ala Val Leu Ala Pro Leu Leu Arg
305                 310                 315                 320
Asp Pro Ala Leu Asp Leu Lys Val Ile His Leu Val Arg Asp Pro Arg
                325                 330                 335
Ala Val Ala Ser Ser Arg Ile Arg Ser Arg His Gly Leu Ile Arg Glu
            340                 345                 350
Ser Leu Gln Val Val Arg Ser Arg Asp Pro Arg Ala His Arg Met Pro
        355                 360                 365
Phe Leu Glu Ala Ala Gly His Lys Leu Gly Ala Lys Lys Glu Gly Val
    370                 375                 380
Gly Gly Pro Ala Asp Tyr His Ala Leu Gly Ala Met Glu Val Ile Cys
385                 390                 395                 400
Asn Ser Met Ala Lys Thr Leu Gln Thr Ala Leu Gln Pro Pro Asp Trp
                405                 410                 415
Leu Gln Gly His Tyr Leu Val Val Arg Tyr Glu Asp Leu Val Gly Asp
            420                 425                 430
Pro Val Lys Thr Leu Arg Arg Val Tyr Asp Phe Val Gly Leu Leu Val
        435                 440                 445
Ser Pro Glu Met Glu Gln Phe Ala Leu Asn Met Thr Ser Gly Ser Gly
    450                 455                 460
Ser Ser Ser Lys Pro Phe Val Val Ser Ala Arg Asn Ala Thr Gln Ala
465                 470                 475                 480
Ala Asn Ala Trp Arg Thr Ala Leu Thr Phe Gln Gln Ile Lys Gln Val
                485                 490                 495
Glu Glu Phe Cys Tyr Gln Pro Met Ala Val Leu Gly Tyr Glu Arg Val
            500                 505                 510
Asn Ser Pro Glu Glu Val Lys Asp Leu Ser Lys Thr Leu Leu Arg Lys
        515                 520                 525
Pro Arg Leu
    530
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<210> 256
<211> 378
<212> PRT
<213> Homo sapiens

<400> 256
Met Arg Arg Leu Asn Arg Lys Lys Thr Leu Ser Leu Val Lys Glu Leu
1 5 10 15
Asp Ala Phe Pro Lys Val Pro Glu Ser Tyr Val Glu Thr Ser Ala Ser
20 25 30
Gly Gly Thr Val Ser Leu Ile Ala Phe Thr Thr Met Ala Leu Leu Thr
35 40 45
Ile Met Glu Phe Ser Val Tyr Gln Asp Thr Trp Met Lys Tyr Glu Tyr
50 55 60
Glu Val Asp Lys Asp Phe Ser Ser Lys Leu Arg Ile Asn Ile Asp Ile
65 70 75 80
Thr Val Ala Met Lys Cys Gln Tyr Val Gly Ala Asp Val Leu Asp Leu
85 90 95
Ala Glu Thr Met Val Ala Ser Ala Asp Gly Leu Val Tyr Glu Pro Thr
100 105 110
Val Phe Asp Leu Ser Pro Gln Gln Lys Glu Trp Gln Arg Met Leu Gln
115 120 125
Leu Ile Gln Ser Arg Leu Gln Glu Glu His Ser Leu Gln Asp Val Ile
130 135 140
Phe Lys Ser Ala Phe Lys Ser Thr Ser Thr Ala Leu Pro Pro Arg Glu
145 150 155 160
Asp Asp Ser Ser Gln Ser Pro Asn Ala Cys Arg Ile His Gly His Leu
165 170 175
Tyr Val Asn Lys Val Ala Gly Asn Phe His Ile Thr Val Gly Lys Ala
180 185 190
Ile Pro His Pro Arg Gly His Ala His Leu Gly Ser Thr Cys Gln Pro
195 200 205
Trp Asn Leu Thr Ile Phe Ser His Arg Ile Asp His Leu Ser Phe Gly
210 215 220
Glu Leu Val Pro Ala Ile Ile Asn Pro Leu Asp Gly Thr Glu Lys Ile
225 230 235 240
Ala Ile Asp His Asn Gln Met Phe Gln Tyr Phe Ile Thr Val Val Pro
245 250 255
Thr Lys Leu His Thr Tyr Lys Ile Ser Ala Asp Thr His Gln Phe Ser
260 265 270
Val Thr Glu Arg Glu Arg Ile Ile Asn His Ala Ala Gly Ser His Gly
275 280 285
Val Ser Gly Ile Phe Met Lys Tyr Asp Leu Ser Ser Leu Met Val Thr
290 295 300
Val Thr Glu Glu His Met Pro Phe Trp Gln Phe Phe Val Arg Leu Cys
305 310 315 320
Gly Ile Val Gly Gly Ile Phe Ser Thr Thr Gly Met Leu His Gly Ile
325 330 335
Gly Lys Phe Ile Val Glu Ile Ile Cys Cys Arg Phe Arg Leu Gly Ser
340 345 350
Tyr Lys Pro Val Asn Ser Val Pro Phe Glu Asp Gly His Thr Asp Asn
355 360 365
His Leu Pro Leu Leu Glu Asn Asn Thr His
370 375

<210> 257
<211> 98

<212> PRT
<213> Homo sapiens

<400> 257
Met Asn Gln Thr Ala Ile Leu Ile Cys Cys Leu Ile Phe Leu Thr Leu
5 10 15
Ser Gly Ile Gln Gly Val Pro Leu Ser Arg Thr Val Arg Cys Thr Cys
20 25 30
Ile Ser Ile Ser Asn Gln Pro Val Asn Pro Arg Ser Leu Glu Lys Leu
35 40 45
Glu Ile Ile Pro Ala Ser Gln Phe Cys Pro Arg Val Glu Ile Ile Ala
50 55 60
Thr Met Lys Lys Lys Gly Glu Lys Arg Cys Leu Asn Pro Glu Ser Lys
65 70 75 80
Ala Ile Lys Asn Leu Leu Lys Ala Val Ser Lys Glu Met Ser Lys Arg
85 90 95
Ser Pro

<210> 258
<211> 530
<212> DNA
<213> Homo sapiens

<400> 258
gaattcggca cgagggctgg aggctgagat gcaggagctc gccatccagc tgcacaagcg 60
ctgcgaggag gtagaggcca cgcggggcca ggtgtgtcag gagcaggagc tgcgcgccgt 120
ggtggagagc tgctgctgga gcaggaccgc gcccgcgagg acctccaggc ccggctgcgg 180
gagacgtggg ccctggcccg ggatgctgcc ctcgtcctgg accagctgcg agcctgtcaa 240
gctgagctgt catctcgagt gaggcaggac cagccccctg gtacagccac tctgggccta 300
gccgtccccc cagctgactc caagggctgg caagcgtccc tgcaggccat gagcctcccc 360
gagctctcgg gagccctgga ggaccgtgtc cgtgagatgg ggcaagcact gtgcttagtg 420
acccagagcc tggagaagct gcaggtgctg aacgggaaga agtggcggga gacctagcct 480
gcgggccgaa tctgacgttg ggtgattggt ccaccctgaa gctgtgtgcc 530

<210> 259
<211> 349
<212> DNA
<213> Homo sapiens

<400> 259
gaattcggca cgaggccagt tcagtctgca agcgccagct cctctcatgg ccggcttacc 60
caccgccttg ccaatgccca ggggcaaacc tcataccacc acttccagaa cactgatcat 120
gacaaccaac aatcaggtac gtggtcctct ggcacccttc ccgctggtgg tccctgggaa 180
cagcatccga gctgtgatat gcactagagg agattgatgg tcctttgaat tagaagagta 240
acttttgag tatttggcca ttggtgtgtt gttctaggaa atcctctctt ttttgtggtg 300
ttgaggtccc ccatgtatag tttcagcagc gaggacactg tggttcttg 349

<210> 260
<211> 509
<212> DNA
<213> Homo sapiens

<400> 260
gaattcggca cgaggcaatc atggcgccac ctgtgagata ctgcatcccc ggcgaacgtc 60
tgtgtaactt ggaggagggc agcccgggca gcggcaccta cacccgccac ggctacatct 120
tttcgtcgct tgccggctgt ctgatgaaga gcagcgagaa tggcgcgctt ccagtggtgt 180
ctgtagtgag agaaacagag tcccagttac tgccagatgt gggagctatt gtaacctgta 240
aggtctctag catcaattca cgctttgcca aagtacacat cctgtatgtg gggtccatgc 300

ctcttaagaa ctcttttcga ggaactatcc gcaaggaaga tgtccgagca actgaaaaag 360
acaaggttga aatttataag agtttccgcc caggtgacat tgtcttggcc aaagtgatct 420
ccttaggtga tgcacagtcc aactacctgc taaccaccgc cgagaacgag ctgggagtgg 480
tggtagccca cagtgagtca ggtatccag 509

<210> 261
<211> 510
<212> DNA
<213> Homo sapiens

<400> 261
gaattcggca cgaggtgcat gttgtgtgag gatcccgggg ccgccgcgtc gctcgggccc 60
cgccatggcc gtcaccatca cgctcaaaac gctgcagcag cagaccttca agatccgcat 120
ggagcctgac gagacggtga aggtgctaaa ggagaagata gaagctgaga agggtcgtga 180
tgccttcccc gtggctggac agaaactcat ctatgccggc aagatcttga gtgacgatgt 240
ccctatcagg gactatcgca tcgatgagaa gaactttgtg gtcgtcatgg tgaccaagac 300
caaagccggc cagggtacct cagcaccccc agaggcctca cccacagctg ccccagagtc 360
ctctacatcc ttcccgcctg cccccacctc aggcatgtcc catcccccac ctgccgccag 420
agaggacaag agcccatcag aggaatccgc ccccacgacg tccccagagt ctgtgtcagg 480
ctcttgttcc ctcttcaggt aacaaccggg 510

<210> 262
<211> 432
<212> DNA
<213> Homo sapiens

<400> 262
gacatgtaat tcttatttat ttttcaccct caacaaggaa gaaaggtctc tccctcaatt 60
ctgctcttcc aatacttgag gataggcacc cctaaccctc cttcctccag ggaggcctca 120
gcatcagtgt ctgtggacgt agtctctgaa gagtgcttca gctgatgggg aaggagaaac 180
tcaagacaga gatcctccta gggatggcgt cactttcctg ccaactttct cgttgcctct 240
ccttgaaagc agaagaagtg ccagccctca gcttccgtca gatcttgggc tcctagggcc 300
ttgtacaagt ccatggccct ctggttccag tccaggacgg ccaggcggaa ttgggagcag 360
cccttatcca aggccacctc agccaccttt ttgattattt tggaaccaat cccttgaccc 420
cgatattccg gc 432

<210> 263
<211> 614
<212> DNA
<213> Homo sapiens

<400> 263
gaattcggca cgaggcgcag agttgtcgct actggagaag tccctgggac tgagtaaggg 60
gaataaatac agtgctcagg gcgagcgaca gattccagtt cttcagacaa acaatggtcc 120
aagtctaaca ggattgacta ctatagcagc tcatctagtc aagcaagcca acaaagaata 180
tttgctgggg agtactgcag aagaaaaagc aatcgttcag cagtggttag aatacagggt 240
cactcaagta gatgggcact ccagtaaaaa tgacatccac acactgttga aggatcttaa 300
ttcatatctt gaagataaag tctaccttac agggtataac tttacattag cagatatact 360
attgtactat ggacttcatc gctttatagt tgacctgaca gttcaagaaa aggagaaata 420
tcttaatgta tctcgctggt tttgtcacat tcagcattat ccaggcatca ggcaacatct 480
gtctagtgtt ggtcttcatc aagaacagac tatatactaa ttcccctaga aagctgtcca 540
tgccatacag aagatctatt aaaaaatgtt ttaaaatgga aaatgtactc ttagaaccac 600
aggacttaat ggta 614

<210> 264
<211> 336
<212> DNA
<213> Homo sapiens

<400> 264
gaattcggca cgaggggcac aacagagccg ctcccctctc ctcgccccgc caccgggacg 60
gagagcgccc gccggtgcat ttccggcgac acctcgcagt cattcctgcg gcttgcgcgc 120
ccttgtagac agccggggcc ttcgtgagaa cggtgcaggc ctggggtagt ctcctgtctg 180
gacagagaag agaaaaatgc aggacactgg ctcaagagtg cctttgcatt ggtttggctt 240
tggctaccca gcactggttg cttctggtgg gaatatttgc tattgaaaag caagcaagcg 300
tgccgtccct ggctgcaggg ctgctctttt ggaagt 336

<210> 265
<211> 487
<212> DNA
<213> Homo sapiens

<400> 265
gaattcggca cgaggtgact gtgggaaact cggaaacaag ctcacatctt cctgtgggaa 60
accttctagc aacaggatga gtctgcagtg gactgcagtt gccaccttcc tctatgcgga 120
ggtctttgtt gtgttgcttc tctgcattcc cttcatttct cctaaaagat ggcagaagat 180
tttcaagtcc cggctggtgg agttgttagt gtcctatggc aacaccttct ttgtggttct 240
cattgtcatc cttgtgctgt tggtcatcga tgccgtgcgc gaaattcgga agtatgatga 300
tgtgacggaa aaggtgaacc tccagaacaa tcccggggcc atggagcact tccacatgaa 360
gcttttccgt gcccagagga atctctacat tgctggcttt tccttgctgc tgtccttcct 420
gcttagacgc ctggtgactc tcatttcgca gcaggccacg ctgctggcct ccaatgaagc 480
ctttaaa 487

<210> 266
<211> 418
<212> DNA
<213> Homo sapiens

<400> 266
gaattcggca cgaggccgtg acctgctagc tgagcagcgc ttcccgggcc gcgtgctgcc 60
ctcggacttg gacctgctgt tgcacatgaa caacgcgcgc tacctgcgcg aggccgactt 120
tgcgcgcgtc gcgcacctga cccgctgcgg ggtgctcggg gcgctgaggg agttgcgggc 180
gcacacggtg ctggcggcct cgtgcgcgcg ccaccgccgc tcgctgcgcc tgctggagcc 240
cttcgaggtg cgcacccgcc tgctgggctg ggacgaccgc gcgttctacc tggaggcgcg 300
ctttgtcagc ctgcgggacg gtttcgtgtg cgcgctgctg cgcttccggc agcacctgct 360
gggcacctca cccgagcgcg tcgtgcagca cctgtgccaa cgcaaggtgg aaccccct 418

<210> 267
<211> 418
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(418)
<223> n = A,T,C or G

<400> 267
gaattcggca cgaggctggc tcccacccgt gagttggctc aacagattga ggaagagacc 60
atcaagtttg ggaaaccgct aggtatccgc actgtggctg tcattggtgg catctccaga 120
gaagaccagg gcttcaggct gcgcatgggt tgtgagattg tgattgctcc cctgggcgtt 180
tgattgatgt gctggaaaac ccgtnccttg tgcttgaccc gctgtaccta tgtggttctg 240
gatgaggcag ataggatgat tgacatgggc tttgagccag atgtccagaa gatcctggag 300
cacatgcctt gtcagcaacc agaagcccaa acacggatga agcttgagga cccctgagaa 360
aaatgcttgg ccaacttttg agtcgggaaa acattaagta cccgcccaaa cagtcatt 418

<210> 268
<211> 266

<212> DNA
<213> Homo sapiens

<400> 268
gaattcggca cgagggcttc tcactgagtg cctactttta tgtcctgcct gtggtgagca 60
caaatgttga gcacatcaat ccccattttg tagacgaaga gacagagttg agtgacttgc 120
ccaaagacac agggccagtg aggagttgtg caggtttgcc ctggcattaa aataataaac 180
attgaaattc agtcgattcc cctatggact cagttataga tctcatcagt tgaaggaaga 240
gagatgcctt ttcctattca accttt 266

<210> 269
<211> 235
<212> DNA
<213> Homo sapiens

<400> 269
gaattcggca cgagggctcc tgcagccttt tcgctgggac tgcgcgacac cgccccccga 60
ccgggtgccc gctgtgtgcc aggccgggtg ctgggcacgg tcccgcgagt gccctataag 120
gactgccagg caataatgaa ggttctttta ctgaaggatg cgaaggaaga tgactgtggc 180
caggatccgt atatcaggga attaggatta tatggacttg aagccacttt gatcc 235

<210> 270
<211> 386
<212> DNA
<213> Homo sapiens

<400> 270
gaattcggca cgagggttcc tcgcgggccg ccgggtgctg gtcaccgggg caggcaaagg 60
tatagggcgc ggcacggtcc aggcgctgca cgcgacgggc gcgcgggtgg tggctgtgag 120
ccggactcag gcggatcttg acagccttgt ccgcgagtgc ccggggatag aacccgtgtg 180
cgtggacctg ggtgactggg aggccaccga gcgggcgctt gggcagcgtg ggccccgtgg 240
acctgctggt gaacaacgcc cgctgtcgcc ctgctgcagc ccttcctgga ggtcaccaag 300
gaggcctttg acagatcctt tgaggtgaac ctgcgtgcgg catccagtgt cacagattgt 360
ggcaggggct taatacccgg gagtcc 386

<210> 271
<211> 406
<212> DNA
<213> Homo sapiens

<400> 271
gaattcggca cgaggggctg ctggctggct aagtccctcc cgctcccggc tctcgcctca 60
ctaggagcgg ctctcggtgc agcgggacag ggcgaagcgg cctgcgccca cggagcgcgc 120
gacactgccc ggaagggacc gccacccttg ccccctcagc tgcccactcg tgatttccag 180
cggcctccgc gcgcgcacga tgccctcggc caccagccac agcgggagcg gcagcaagtc 240
gtccggaccg ccaccgccgt cgggttcctc cgggagtgag gcggccgcgg gagccggggc 300
cgccgcgccg gcttctagca ccccgcaacc ggcaccggcg ctgtccagac cgaggccatg 360
aagcagattc tcggggtgat cgacaagaaa cttcggaacc tggaga 406

<210> 272
<211> 365
<212> DNA
<213> Homo sapiens

<400> 272
gaattcggca cgaggctcgc ctcactagga gcggctctcg gtgcagcggg acagggcgaa 60
gcggcctgcg cccacggagc gcgcgacact gcccggaagg gaccgccacc cttgcccccc 120
cagctgccca ctcgtgattt ccagcggcct ccgcgcgcgc acgatgccct cggccaccag 180
ccacagcggg agcggcagca agtcgtccgg accgccaccg ccgtcgggtt cctccgggag 240

tgaggcggcc gcgggagccg gggccgcgcg ccggcttcta gcaccccgca accggcaccg 300
gcgctgtcca gaccgaggcc atgaagcaga ttctcggggt gatcgacaag aaacttcgga 360
acctg 365

<210> 273
<211> 376
<212> DNA
<213> Homo sapiens

<400> 273
gaattcggca cgaggctttg gccactcaga gcccccgggc cgcggtcgtc gtacgcctga 60
aggcgggtcg tgccggcggc cgctctagtc tccgcctccg ctcaggccgg tcctccgggg 120
cttctcaatg gtttcccggt ggcctctcaa tggttttccc ggcggccctt gcgccgacgc 180
caggagactt ccggagcttg gtgacgtcac agagcgagct tttctaccca aatacgcggc 240
gggggaatag gctcgagggc ggggagcagt gacaattgct aggcggagac agtgcaggga 300
agagagacct tataaaggat caggactggc gggaggtatt taactgaaag gaatatctgc 360
ttcactgttg caacca 376

<210> 274
<211> 385
<212> DNA
<213> Homo sapiens

<400> 274
gaattcggca cgaggcttgg gtccgtcgct gcttcggtgt ccctgtcggg cttcccagca 60
gcggcctagc gggaaaagta aaagatgtct gaatatattc gggtaaccga agatgagaac 120
gatgagccca ttgaaatacc atcggaagac gatgggacgg tgctgctctc cacggttaca 180
gcccagtttc caggggcgtg tgggcttcgc tacaggaatc cagtgtctca gtgtatgaga 240
ggtgtccggc tggtagaagg aattctgcat gccccagatg ctggctgggg aaatctggtg 300
tatgttgtca actatccaaa agataacaaa agaaaaatgg atgagacaga tgcttcatca 360
gcagtgaaag tgaaaagagc agtcc 385

<210> 275
<211> 395
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(395)
<223> n = A,T,C or G

<400> 275
gaattcggca cgagggggag cggagagcgg accccagaga gccctgagca gccccaccgc 60
cgccgccggc ctagttacca tcacaccccg ggaggagccg cagctgccgc agccggcccc 120
agtcaccatc accgcaacca tgagcagcga ggccgagacc cagcagccgc ccgccgcccc 180
ccccgccgcc cccgccctca gcgccgccga caccaagccc ggcactacgg gcagcggcgc 240
aaggagcggt ggcccgggcg gcctcacatt cggcggggcc ttgccggcgg ggacaaagaa 300
agggcattcg caacgaaggg ttttgggaaa caagtaaaat gggttcaatt gtaagggaac 360
cggattttgg ttttnattca accagggaaa ttgac 395

<210> 276
<211> 282
<212> DNA
<213> Homo sapiens

<400> 276
gaattcggca cgagggcagg ggtggtcctg gctggcattg cctgagccgg cagtgatgaa 60
gtggggagct tgcccttgac aggtgggggc tggctggggc cttaatgtga aaagacagtg 120

gcaggcagct ggagtagagc gagcccagca gccctaaaag gctgccttca tggccatcta 180
gccccagttc agggcagcat ccatagccca caagccagcg tgggtggggc gggggtggtc 240
ccacagctgg gttccacctg aagagcctcc gtgcctcgga gc 282

<210> 277
<211> 615
<212> DNA
<213> Homo sapiens

<400> 277
gaattcggca cgaggccggt cggcctgggc aacctgcgct gaagatgccg ggaaaactcc 60
gtagtgacgc tggtttggaa tcagacaccg caatgaaaaa aggggagaca ctgcgaaagc 120
aaaccgagga gaaagagaaa aaagagaagc caaaatctga taagactgaa gagatagcag 180
aagaggaaga aactgttttc cccaaagcta aacaagttaa aaagaaagca gagccttctg 240
aagttgacat gaattctcct aaatccaaaa aggcaaaaaa gaaagaggag ccatctcaaa 300
atgacatttc tcctaaaacc aaaagtttga gaaagaaaaa ggagcccatt gaaaagaaag 360
tggtttcttc taaaaccaaa aaagtgacaa aaaatgagga gccttctgag gaagaaatag 420
atgctcctaa gcccaagaag atgaagaaag aaaaggaaat gaatggagaa actagagaga 480
aaagccccaa actgaagaat ggatttcctc atcctgaacc ggactgtaac cccagtgaag 540
ctgccagtga agaaagtaac agtgagatag agcaggaaat cctgtggaac aaaaagaagg 600
cgctttctct atttt 615

<210> 278
<211> 316
<212> DNA
<213> Homo sapiens

<400> 278
gaattcggca cgaggagaaa gggaaaaaag gcgtaaagac agacatgaag caagtgggtt 60
tgcaaggaga ccagatccag attctgatga agatgaagat tatgagcgag agaggaggaa 120
aagaagtatg ggcggagctg ccattgcccc acccacttct ctggtagaga aagacaaaga 180
gttaccccga gattttcctt atgaagaagg actcaagacc tcgatcacag tctttccaag 240
cagccctttc ttcccccagt gtaccgaagg aaccaagaac agacccgaga atcttccacc 300
cggaccctta gcaaac 316

<210> 279
<211> 393
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(393)
<223> n = A,T,C or G

<400> 279
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gtgttaccag gtttgcccca gtacaccagc atatatacac ccttggccag cctttctcct 180
gaatatcagc taccaagatc agtaccagtg gtgccgtctt ttgtagccaa tgacagagca 240
gaaaaaaatg ctggctgcct attttgnggg gcattcattt tgaaatggct tgagaaatgg 300
ttggctgggt cacccagaat tggccttctt gaaaaccaca agaatccctt tggaaggggg 360
cttctttttg gggaaaataa tcttggtaaa aag 393

<210> 280
<211> 454
<212> DNA
<213> Homo sapiens

<400> 280
gaattcggca cgaggcagca atgcggtaga tatgacgtaa acaaattata attaagctag 60
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tttttcatga tgtctaactc tactgaattt attcaatgga gataacagaa agatgattat 180
atatgattaa attacttcca gtattagcag atgcttattt aaatacttgc ttgttctttc 240
tgcaattcca catagaatta aggcaatagt ttaaaagaaa atttaaaaag taacttttct 300
agcattttaa tgtagacctg tgaattctaa cacatttgca gtgtagccat cctaatgact 360
aaccagactt gaacaaaatc caacttgcaa aaacgatgca atataaatac caatcaccaa 420
taataggtag tctcactttt aaaaacctgt gtct 454

<210> 281
<211> 613
<212> DNA
<213> Homo sapiens

<400> 281
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ggaggaagcg taaggctgag gccgcggtgg tcgccgtagc cgagaagcga gagaagctgg 180
cgaacggcgg ggagggaatg gaggaggcga ccgttgttat cgagcattgc actagctgac 240
gcgtctatgg gcgcaacgcc gcggccctga gccaggcgct gcgcctggag gccccagagc 300
ttccagtaaa ggtgaacccg acgaagcccc ggaggggcag cttcgaggtg acgctgctgc 360
gcccggacgg cagcagtgcg gagctctgga ctgggattaa gaaggggccc ccacgcaaac 420
tcaaattccc tgagcctcaa gaggtggtgg aagagttgaa gaagtacctg tcgtagggag 480
atttgggtag aagccctcat gctgagcttt gtgtccctgg tgatgttgga acattaatga 540
tggaacatgg ccaaacttca gtcatgatcc tgaagccatg gtttcttccc tgccagaaat 600
gaaggttcat tat 613

<210> 282
<211> 313
<212> DNA
<213> Homo sapiens

<400> 282
gaattcggca cgaggcgaga acgggcacgg ggagcagcag cctcaaccgc cggcgacgca 60
gcagcaacag ccccaacagc agcgcggggc cgccaaggag gccgcgggga agagcagcgg 120
ccccacctcg ctgttcgcgg tgacggtggc gccgcccggg gcgaggcagg gccagcagca 180
ggcgggaggt aagaagaagg cggaaggcgg cggaggcggc ggtcgccccg gggctccggc 240
ggcgggggac ggcaaaacag aacagaaagg cggagataaa aagaggggtg ttaaaagacc 300
accacaagat cat 313

<210> 283
<211> 557
<212> DNA
<213> Homo sapiens

<400> 283
gaattcggca cgaggcctgg ccggggagac gagttgcatg tgttggttca gctggcgata 60
gcggcgggag cggagccggc ggggcctgtg cgaccgcctg ggtttgtgaa atggctgctg 120
acatttctga atccagcggg gctgactgca aaggagaccc aaggaacagt gccaagttag 180
atgccgatta cccacttcga gtcctttatt gtggagtctg ttcattacca acagagtact 240
gtgaatatat gcctgatgtt gctaaatgta gacaatggtt agagaagaat tttccaaatg 300
aatttgcaaa acttactgta gaaaattcac ccaaacaaga agctggaatt agtgagggtc 360
aaggaacagc aggggaagaa gaggagaaga aaaaacagaa gagaggtgga aggggtcaaa 420
taaaacaaaa aaagaagacc gtaccacaaa aggttactat agccaaaatt cccagagcaa 480
agaagaaata tgtgacaaga gtatgtggcc ttgcaacttt tgaaattgat cttaaagaag 540
cacaaagatt ttttgct 557

<210> 284

<211> 627
<212> DNA
<213> Homo sapiens

<400> 284
gaattcggca cgaggctcac taggagcggc tctcggtgca gcgggacagg gcgaagcggc 60
ctgcgcccac ggagcgcgcg acactgcccg gaagggaccg ccacccttgc cccctcagct 120
gcccactcgt gatttccagc ggcctccgcg cgcgcacgat gccctcggcc accagccaca 180
gcgggagcgg cagcaagtcg tccggaccgc caccgccgtc gggttcctcc gggagtgagg 240
cggccgcggg agccggggcc gccgcgccgg cttctcagca ccccgcaacc ggcaccggcg 300
ctgtccagac cgaggccatg aagcagattc tcggggtgat cgacaagaaa cttcggaacc 360
tggagaagaa aaagggtaag cttgatgatt accaggaacg aatgaacaaa ggggaaaggc 420
ttaatcaaga tcagctggat gccgtttcta agtaccagga agtcacaaat aatttggagt 480
ttgcaaaaga attacagagg agtttcatgg cactaagtca agatattcag aaaacaataa 540
agaagacagc acgtcgggag cagcttatga aaaaagaact gaacagaaac gtttaaaaac 600
ttgtacttga actacagtat tgtttgg 627

<210> 285
<211> 474
<212> DNA
<213> Homo sapiens

<400> 285
gaattcggca cgagggcgag aacgaccccc ggaccgacca aagcccgcgc gccgctgcat 60
cccgcgtcca gcacctacgt cccgctgccg tcgccgccgc caccatgccc aagagaaagg 120
ctgaagggga tgctaaggga gataaagcaa aggtgaagga cgaaccacag agaagatccg 180
cgaggttgtc tgctaaacct gctcctccaa agccagagcc caagcctaaa aaggcccctg 240
caaagaaggg agagaaggta cccaaaggga aaaagggaaa agctgatgct ggcaaggagg 300
ggaataaccc tgcagaaaat ggagatgcca aaacagacca ggcacagaaa gctgaaggtg 360
ctggagatgc caagtgaagt gtgtgcattt ttgataactg tgtacttctg gtgactgtac 420
agtttgaaat actatttttt atcaagtttt ataaaaatgc agaattttgg ttta 474

<210> 286
<211> 576
<212> DNA
<213> Homo sapiens

<400> 286
gaattcggca cgaggggaat ctgtgaagct cactactgga ccaaacaacg ctggagctca 60
aagtagttct tcatgtggga cttctggcct tccagtttct gcacagacag ccttggcaga 120
acaacagcca aaaagcatga aaagcccagc ttctccagag cctggtttct gtgctactct 180
ttgccctatg gtagaaattc cacctaaaga tataatggca gaattggagt cagaggatat 240
cttgatccct gaagaatctg taattcagga ggaaattgca gaagaggtag agactagtat 300
ctgtgaatgc caggatgaaa atcataagac aatacctgaa ttttctgagg aggctgaaag 360
tctaaccaat tctcatgaag aaccccaaat agcacctcct gaagataact tggaatcctg 420
tgttatgatg aatgatgttt tagaaacttt gcctcatatt gaagttaaga tagaagggaa 480
gtcagaatca ccccaggaag aaatgacagt tgttatcgat cagttagaag tctgtgactc 540
tcttattcct tccacttcat ctatgactca tgtcag 576

<210> 287
<211> 514
<212> DNA
<213> Homo sapiens

<400> 287
gaattcggca cgaggcagag aggtttgcca aagagcgcag gctgagaata tggagagact 60
atgtggctcc cacagctaat ttggaccaaa aggacaagca gtttgttgcc aaggtgatgc 120
aggttctgaa tgctgatgcc attgttgtga agctgaactc aggcgattac aagacgattc 180
acctgtccag catccgacca ccgaggctgg agggggagaa cacccaggat aagaacaaga 240

aactgcgtcc cctgtatgac attccttaca tgtttgaggc ccgggaattt cttcgaaaaa 300
agcttattgg gaagaaggtc aatgtgacgg tggactacat tagaccagcc agcccagcca 360
cagagacagt gcctgccttt tcagagcgta cctgtgccac tgtcaccatt ggaggaataa 420
acattgctga ggctcttgtc agcaaaggtc tagccacagt gatcagatac cggcaggatg 480
atgaccagag atcatcacac tacgatgaac tgct 514

<210> 288
<211> 456
<212> DNA
<213> Homo sapiens

<400> 288
gaattcggca cgaggggcg ggcaggcggg caggccggca ggcgggtgcg cggagggctg 60
gtgccccgca gcaggtgggc ggggtgcggt tggcggcggc ggctgggccg ggggctgccg 120
gctgcgctcg ggccgtgcgc ggcggccgtg cgggcacgcc atggacttca acatgaagaa 180
gctggcgtcg gacgcgggca tcttcttcac ccgggcggtg cagttcacgg aggagaaatt 240
tggccaggct gagaagactg agcttgatgc ccactttgaa aaccttctgg cccgggcaga 300
cagcaccaag aactggacag agaagatctt gaggcagaca gaggtgctgc tgcagcccaa 360
ccccagtgcc cgagtggagg agttcctgta tgagaagctg gacaggaagg tcccctcaag 420
ggtcaccaac ggggagctgc tggctcagta catggc 456

<210> 289
<211> 262
<212> DNA
<213> Homo sapiens

<400> 289
gaattcggca cgaggcagaa gcccctagct cctctgagcc tcatggggcc agaggaagca 60
gtagttcggg cggcaagaaa tgctacaagc tggagaatga gaagctgttc gaagagttcc 120
ttgaactttg taagatgcag acagcagacc accctgaggt ggtcccattc ctctataacc 180
ggcagcaacg tgcccactct ctgtttttgg cctcggcgga gttctgcaac atcctctcta 240
gggtcctgtc tcgggcccgg ac 262

<210> 290
<211> 205
<212> DNA
<213> Homo sapiens

<400> 290
gaattcggca cgaggattta tgggccactg cacatgcccg ctgcagccct gggatcagct 60
ggaagctgcc tgtcatctcc tgcccaatcc ccagaaaccc tgattcaggt ctgcaggctc 120
ctgcgggctc accaggctgc tggctccggt accatgtaaa cctaggaagg taaaggagca 180
ggcaacctcc tcgtggcctg tgtgt 205

<210> 291
<211> 483
<212> DNA
<213> Homo sapiens

<400> 291
gaattcggca cgaggcctgg ccgggaccgt gtgggccgtg aggatgagga cggctgggag 60
acgcgagggg accgcaaggc ccggaagccc ctggtggaga agaagcggcg cgcgcggatc 120
aacgagagcc tgcaggagct gcggctgctg ctggcgggcg ccgaggtgca ggccaagctg 180
gagaacgccg aagtgctgga gctgacggtg cggcgggtcc agggtgtgct gcggggccgg 240
gcgcgcgagc gcgagcagct gcaggcggaa gcgagcgaac gcttcgctgc cggctacatc 300
cagtgcatgc acgaggtgca cacgttcgtg tccacgtgcc aggccatcga cgctaccgtt 360
ctgccgagct cctgaaccat ctgctcgagt ccatgccgct gcgtgagggc agcaacttca 420
ggatctgctg ggggacgccc tgcggggcca cctaaatccc ctggacggaa tggctggctg 480
cgg 483

<210> 292
<211> 562
<212> DNA
<213> Homo sapiens

<400> 292
gaattcggca cgagggcgct gcgggtagga gccgggttgc gggagacccc aggttcggtt 60
gggattccca gccagaacgg agcttaagcc gggcaggcga gcgaatgacg gagtagcgag 120
ctgcacggcg gcgtgctgcg ctgttgagga cgctgtcccg cgcgctccca ggccgccccg 180
aggcttgggg tcttcgaagg ataatcggcg cccggggccg aacagcgggg gcacacgggg 240
cgctgccgaa gtgcaaggcc acggccagag ctcgagcccg acgcgctgtc tggagtcgta 300
ggttggcgcc gtttggggtc ggggtctgag gcttgggcgc tgcctgggcc gagcggagat 360
cggggtttgc ctcccgtccc cgctcaggac cctgacgtgg ctgaagcggc cccgggagca 420
tgagcggcag cgcgtggacg tcaaggtggt gatgctgggc aaggagtacg tgggcaagac 480
tagcctggtg gagcgctacg tgcacgaccg ctttctggtg gggccttatc agaacaccat 540
cggggccgcc ttcgtggcca ag 562

<210> 293
<211> 645
<212> DNA
<213> Homo sapiens

<400> 293
gaattcggca cgaggctgag agagagcaca gcctggtggg ttctggggtc tacggcctag 60
gggccgggga agtttgcgcc gccgcgacca gtgctgcgat cccgagccgg gctccagccc 120
cgaggaccag gggtcgggcg ggcctgccta cggaaccccg cgggccagca gcagtcgtct 180
cgcgtcctcc tgcttggaaa agtgtttaag cttctaaaat gtcatctatc aagcacctgg 240
tttatgcagt tattcgtttc ttacgggaac aaagtcagat ggacacttac acctcggatg 300
aacaagaaag tttggaagtt gcaattcagt gcttggagac agtttttaag atcagcccag 360
aagatacaca cctagcagtt tcacagcctt tgacagaaat gtttaccagt tccttctgta 420
agaatgacgt tctgcccctt tcaaactcag tgcctgaaga tgtgggaaaa gctgaccaat 480
taaaagatga aggcaataac cacatgaaag aagaaaatta tgctgctgca gtggattgtt 540
acacacaggc aatagaattg gatcccaata atgcagttta ctattgcaac agggctgctg 600
ctcagagcaa attaggtcac tacacagatg cgataaagga ttgtg 645

<210> 294
<211> 521
<212> DNA
<213> Homo sapiens

<400> 294
ctgagcgtct ctgcttagcc gcggtcatga gccggcacag ccggctgcag aggcaggttc 60
tgagcctgta ccgcgatctg ctgcgcgccg ggcgtgggaa gccgggcgcc gaggcgcgag 120
tgcgggcaga gttccggcag catgcgggcc tgccgcggtc cgacgtgctg cgcatcgagt 180
acctgtaccg ccgcgggcgg cgccagctgc agctgctacg ctcgggccac gccaccgcca 240
tgggcgcctt cgtacgcccg cgggccccga ccggggagcc tggcggcgtg ggttcccagc 300
ctgacgacgg cgacagtcca aggaaccccc acgacagcac gggggcaccg gagacccgcc 360
ccgacggacg gtgacaggcg aagagccgaa ctcgctcgat ggcgtggtgg agccaggagg 420
ctcgcctgac tgcatggggg gactggggaa cccgcctaag gtgagaggtc ttaagagact 480
agcttgacga attggggatg tcagagactc ctccttggcg a 521

<210> 295
<211> 375
<212> DNA
<213> Homo sapiens

<400> 295
gaattcggca cgaggagaac atgcagtcta ggaaccggca tgcgcataac ctcaggatat 60

aaataatgct gaagcagagt tacgtttttt ttgttgttgt ttttttgtt tttgtttttt 120
taggtttccg tgtgtttcta ttgagctgct cagtgcccgg cttagaagac caggaaaagg 180
agtcacaggt cgtatgctgg aggcttgagc cgcggcaccg tggcgcggct cgcctcgctg 240
cggttggtgg tggcggtgga cattgcagcg cggctggagg gggtccttag acaaggtgca 300
agacaaacag aagagggcat gtggggtcaa actcctactg cctgcctgat tttctgccac 360
aggacaaatt cacca 375

<210> 296
<211> 628
<212> DNA
<213> Homo sapiens

<400> 296
gaattcggca cgaggaaaat ggttcgctat tcacttgacc cggagaaccc cacgaaatca 60
tgcaaatcaa gaggttccaa tcttcgtgtt cactttaaga acactcgtga aactgctcag 120
gccatcaagg gtatgcatat acgaaaagcc acgaagtatc tgaaagatgt cactttacag 180
aaacagtgtg taccattccg acgttacaat ggtggagttg gcaggtgtgc gcaggccaag 240
caatggggct ggacacaagg tcggtggccc aaaaagagtg ctgaattttt gctgcacatg 300
cttaaaaacg cagagagtaa tgctgaactt aagggtttag atgtagattc tctggtcatt 360
gagcatatcc aagtgaacaa agcacctaag atgcgccgcc ggacctacag agctcatggt 420
cggattaacc catacatgag ctctccctgc cacattgaga tgatccttac ggaaaaggaa 480
cagattgttc ctaaaccaga agaggaggtt gcccagaaga aaaagatatc ccagaagaaa 540
ctgaagaaac caaaacttat ggcacgggag taaattctca ttaaaataaa tgtaattaaa 600
aggaaaaaaa aaaaaaaaaa aactcgag 628

<210> 297
<211> 645
<212> DNA
<213> Homo sapiens

<400> 297
gaattcggca cgaggagaaa acgaagcagc gttggaaaat ggaattaaaa atgaggaaaa 60
cacagaacca ggtgctgaat cttctgagaa cgctgatgat cccaacaaag atacaagtga 120
aaacgcagat ggtcaaagtg atgagaacaa ggacgactat acaatcccag atgagtatag 180
aattggacca tatcagccca atgttcctgt tggtatagac tatgtgatac ctaaaacagg 240
gttttactgt aagctgtgtt cactctttta tacaaatgaa gaagttgcaa agaatactca 300
ttgcagcagc cttcctcatt atcagaaatt aaagaaattt ctgaataaat tggcagaaga 360
acgcagacag aagaaggaaa cttaagatgt gcaaggagat ttaatgattt caaagaaaat 420
aatggttctt tgtttttaat gttaaccttt tttaaataca atactgatag ttagaagaaa 480
actattgtac tcttttgttt tagtggagaa ataatagatg tctgttcatg tgttaagtgt 540
tatagcaaaa aaaatacaca tatggttaag ttaatgaata gtttttgttt tatcagaatg 600
gcaacagaca gaagtacttt gtagagattg acttcctaag ctctt 645

<210> 298
<211> 625
<212> DNA
<213> Homo sapiens

<400> 298
gaattcggca cgaggggatt cagcagcctc ccccttgagc cccctcgctt cccgacgttc 60
cgttcccccc tgcccgcctt ctcccgccac cgccgccgcc gccttccgca ggccgtttcc 120
accgaggaaa aggaatcgta tcgtatgtcc gctatccaga acctccactc tttcgacccc 180
tttgctgatg caagtaaggg tgatgacctg cttcctgctg gcactgagga ttatatccat 240
ataagaattc aacagagaaa cggcaggaag acccttacta ctgtccaagg gatcgctgat 300
gattacgata aaaagaaact agtgaaggcg tttaagaaaa agtttgcctg caatggtact 360
gtaattgagc atccggaata tggagaagta attcagctac agggtgacca acgcaagaac 420
atatgccagt tcctcgtaga gattggactg gctaaggacg atcagctgaa ggttcatggg 480
ttttaagtgc ttgtggctca ctgaagctta agtgaggatt tccttgcaat gagtagaatt 540
tcccttctct tccttgtcac aggtttaaaa acctcacagc ttgtataatg taaccatttg 600

gggtccgctt ttaacttgga ctagt 625

<210> 299
<211> 545
<212> DNA
<213> Homo sapiens

<400> 299
gaattcggca cgagggagcc caggaggtca aggctacagt gagccgtgat catgccactg 60
cactccagcc tgggtgacag agcgagaccc tgtctcttaa caacaaaacc catgagcggc 120
agcccccag tcctggatgg tggtaaagaa tcctcaagat caaacccacg cagtgctgag 180
agcttggcct gattctaggg ctggggctgg agaaactgct agagatgatg ccgatagcca 240
gtgtgatccc cctgccctga tggtcaaggg cagagtgcag actggaaccc tcccctcccc 300
aaagattcag acctgtgggg ctgagtgggc tcatagtgtc cccaagtcct gagaggctgg 360
tgtctggctt cagcctccag cttctcaggt tctgatgcag tcagctgagt tccctgccta 420
ttcttgcaag cactaggagg aagggtggtg ggttgctggg aacagcaccg agcgccctcc 480
ccacccagat tcacagagca cactccccgg ggggatactt taatccggag gccgtgacgc 540
ctgct 545

<210> 300
<211> 605
<212> DNA
<213> Homo sapiens

<400> 300
gaattgggca cgaggcgggc cgcagctttt cggttcacag cgggcaggga aagccgcggg 60
aagggtactc caggcgagag gcggacgcga gtcgtcgtgg caggaaaagt gactagctcc 120
ccttcgttgt cagccaggga cgagaacaca gccacgctcc cacccggctg ccaacgatcc 180
ctcggcggcg atgtcggccg ccggtgcccg aggcctgcgg gccacctacc accggctcct 240
cgataaagtg gagctgatgc tgcccgagaa attgaggccg ttgtacaacc atccagcagg 300
tcccagaaca gtttttttct gggctccaat tatgaaatgg gggttggtgt gtgctggatt 360
ggctgatatg gccagacctg cagaaaaact tagcacagct caatctgctg ttttgatggc 420
tacagggttt atttggtcaa gatactcact tgtaattatt ccaaaaaatt ggagtctgtt 480
tgctgttaat ttctttgtgg gggcagcagg agcctctcag ctttttcgta tttggagata 540
taaccaagac taaaagctaa agcacacaaa taaaagagtt ctgatcacct gaacaatcta 600
gatgt 605

<210> 301
<211> 364
<212> DNA
<213> Homo sapiens

<400> 301
gaattcggca cgaggcgcac acgagaacat gcctctcgca aaggatctcc ttcatccctc 60
tccagaagag gagaagagga aacacaagaa gaaacgcctg gtgcagagcc ccaattccta 120
cttcatggat gtgaaatgcc caggatgcta taaaatcacc acggtcttta gccatgcaca 180
aacggtagtt ttgtgtgttg gctgctccac tgtcctctgc cagcctacag gaggaaaagc 240
aaggcttaca gaaggatgtt ccttcaggag gaagcagcac taaaagcact ctgagtcaag 300
atgagtggga aaccatctca ataaacacat tttggataaa aaaaaaaaaa aaaaaaaact 360
cgag 364

<210> 302
<211> 545
<212> DNA
<213> Homo sapiens

<400> 302
gaattccggc acgaggggac cccagagagc cctgagcagc cccaccgccg ccgccggcct 60
agttaccatc acaccccggg aggagccgca gctgccgcag ccggccccag tcaccatcac 120

cgcaaccatg agcagcgagg ccgagaccca gcagccgccc gccgcccccc ccgccgcccc 180
cgccctcagc gccgccgaca ccaagcccgg cactacgggc agcggcgcag ggagcggtgg 240
cccggggcggc ctcacatcgg cggcgcctgc cggcggggac aagaaggtca tcgcaacgaa 300
ggttttggga acagtaaaat ggttcaatgt aaggaacgga tatggtttca tcaacaggaa 360
tgacaccaag gaagatgtat ttgtacacca gactgccata aagaagaata accccaggaa 420
gtaccttcgc agtgtaggag atggagagac tgtggagttt gatgttgttg aaggagaaaa 480
gggtgcggag gcagcaaatg ttacaggtcc tggtggtgtt ccagttcaag gcagtaaata 540
tgcag 545

<210> 303
<211> 506
<212> DNA
<213> Homo sapiens

<400> 303
gaattcggca cgaggctggt cactccgcca ccgtagaatc gcctaccatt tggtgcaagc 60
aaaaagcaat cagcaattgg acaggaaaag aatggcattg aagcagattt ccagcaacaa 120
gtgctttggg ggattgcaga aagtttttga acatgacagt gttgaactaa actgcaaaat 180
gaaatttgct gtctacttac caccaaaggc agaaacagga aagtgccctg cactgtattg 240
gctctcaggt ttaacttgca cagagcaaaa ttttatatca aaatctggtt atcatcagtc 300
tgcttcagaa catggtcttg ttgtcattgc tccagatacc agccctcgtg gctgcaatat 360
taaaggtgaa gatgagagct gggactttgg cactggtgct ggattttatg ttgatgccac 420
tgaagatcct tggaaaacca actacagaat gtactcttat gtcacagagg agcttcccca 480
actcataaat gccaattttc cagtgg 506

<210> 304
<211> 485
<212> DNA
<213> Homo sapiens

<400> 304
gaattcggca cgagggagtt gtgggcccag gagccctgcg gctgccggca ggtgaactga 60
gtgcccgaca gctgagaccg gcgcccaccc gtcctgagca tagctctgta ggcagtgcgg 120
gcatagcctg catagtgtcc tggcgctggg agttccccgt ggacagagcc agagggcagt 180
ggcgctccct gtcagagctg gatcaggccc cccatcgagg agggagggca gacggaggcc 240
cgagagcctc cccaggcctc ttcgtgggaa ggccccagta ccactcgtag gaggtctcag 300
ctctggcatg gctgccccgg atgtggccga gggggcttca ccctgtgtcc ttaggagggg 360
gtggccttga ggcaagagcc gtgcctcact gacccccagg ggcctcatcc tccccatgga 420
atgggctgta tgtcctgccc caacttggcc cgcagcaggc cagacccccc taccccccgcc 480
cagag 485

<210> 305
<211> 615
<212> DNA
<213> Homo sapiens

<400> 305
gaattcggca cgaggcttac aaggaaaatg ctgacttatg accggcgctc tgagcctcag 60
gttggggagc gagtgccata cgtcatcatt tatgggaccc ccggagtacc acttatccag 120
cttgtaaggc gcccagtgga agtcctgcag gacccaactc tgagactgaa tgctacttac 180
tatattacca agcaaatcct tccacccttg gcaagaatct tctcacttat tggtattgat 240
gtcttcagct ggtatcatga attaccaagg atccataaag ctaccagctc ctcgcgaagt 300
gaacctgaag ggcggaaagg cactatttca caatatttta ctaccttaca ctgtcctgtg 360
tgtgatgacc taactcagca tggcatctgt agtaaatgtc ggagccaacc tcagcatgtt 420
gcagtcatcc tcaaccaaga aatccgggag ttggaacgtc aacaggagca acttgtaaag 480
atatgcaaga actgtacagg ttgctttgat cgacacatcc catgtgtttc tctgaactgc 540
ccagtacttt tcaaactctt ccgagtaaat agagaattgt ccaaggcacc atatcttcgg 600
cagttattaa accag 615

<210> 306
<211> 504
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(504)
<223> n = A,T,C or G

<400> 306
gaattcggca cnaggccaaa acctgtttgg gaagcatatt acagaaatga tttcaagtac 60
cctgtattct ggatgctaaa aaacaaaaac aaacaaaaaa acaaaaacaa aaaaacaaaa 120
ccagaatcag gtaaaacagc tatgtgatta aaatatttta attcttcagc aattacccgg 180
ttttctaaat tgaatcatgc atctatttat aattctaatt attttgtaaa agaagacaaa 240
attatgaatc ttaagtattt gctccatctt tttctctgta atggtggaga ggctgcccat 300
aattcatctc cacatggagc caagtttaat gtttctagtt cacattttgt acttctgtca 360
tgcttatttc aaactccctg agtgatgggt aagaaatcaa acattgcctc agtggtatca 420
agagaacttt ggtggtggtt tcttcagaat catgaagttc ttttgccaga taaatatttt 480
gatattattt tccttttaa tata 504

<210> 307
<211> 449
<212> DNA
<213> Homo sapiens

<400> 307
gaattcggca cgaggtttaa accctgcgtg gcaatccctg acgcaccgcc gtgatgccca 60
gggaagacag ggcgacctgg aagtccaact acttccttaa gatcatccaa ctattggatg 120
attatccgaa atgtttcatt gtgggagcag acaatgtggg ctccaagcag atgcagcaga 180
tccgcatgtc ccttcgcggg aaggctgtgg tgctgatggg caagaacacc atgatgcgca 240
aggccatccg agggcacctg gaaaacaacc cagctctgga gaaactgctg cctcatatcc 300
gggggaatgt gggctttgtg ttcaccaagg aggacctcac tgagatcagg gacatgttgc 360
tggccaataa ggtgccagct gctgccgtgc tggtgccatt gccccatgtg aagtcactgt 420
gccagcccag aacactggtc tcgggcccg 449

<210> 308
<211> 524
<212> DNA
<213> Homo sapiens

<400> 308
gaattcggca cgagggttga ttatggcaag aagtccaagc tggagttctc catttaccca 60
gcaccccagg tttccacagc tgtagttgag ccctacaact ccatcctcac cacccacacc 120
accctggagc actctgattg tgccttcatg gtagacaatg aggccatcta tgacatctgt 180
cgtagaaacc tcgatatcga gcgcccaacc tacactaacc ttaaccgcct tattagccag 240
attgtgtcct ccatcactgc ttccctgaga tttgatggag ccctgaatgt tgacctgaca 300
gaattccaga ccaacctggt gccctacccc cgcatccact tccctctggc cacatatgcc 360
cctgtcatct ctgctgagaa agcctaccat gaacagcttt ctgtagcaga gatcaccaat 420
gcttgctttg agccagccaa ccagatggtg aaatgtgacc ctcgccatgg taaatacatg 480
gcttgctgcc tgttgtaccg tggtgacgtg gttcccaaag atgt 524

<210> 309
<211> 524
<212> DNA
<213> Homo sapiens

<400> 309
gaattcggca cgagggcttc tcactgagtg cctactttta tgtcctgcct gtggtgagca 60

caaatgttga gcacatcaat ccccattttg tagacgaaga gacagagttg agtgacttgc 120
ccaaagacac agggccagtg aggagttgtg caggtttgcc ctggcattaa aataataaac 180
attgaaattc agtcgattcc cctatggact cagttataga tctcatcagt tgaaggaaga 240
gagatgcctt ttcctattca gccttttgc aatccttcca tctagaggag atgtatctta 300
taatatcctc aaaggcactc tgttgctaat agcagccttg atgaggtccc atatagctca 360
ttggaagcag agctagtctt ggaaactgaa aatgttggac cagagtctgc ccattccttt 420
agctctgggt ccagctgtgg tctggggtgg aatggagtct gaccttgcct cacacagggc 480
ctgtctgttc tcattgtggc catccacatc ctggagctgc tcat 524

<210> 310
<211> 524
<212> DNA
<213> Homo sapiens

<400> 310
gaattcggca cgaggggaga ctacaaggat aggcccagga gtaatggagt ccaaagagaa 60
acgagcagta aacagtctca gcatggaaaa tgccaaccaa gaaaatgaag aaaaggagca 120
agttgctaat aaaggggagc ccttggccct ccctttggat gctggtgaat actgtgtgcc 180
tagaggaaat cgtaggcggt tccgcgttag gcagcccatc ctgcagtata gatgggatat 240
gatgcatagg cttggagaac cacaggcaag gatgagagaa gagaatatgg aaaggattgg 300
ggaggaggtg agacagctga tggaaaagct gagggaaaag cagttgagtc atagtctgcg 360
ggcagtcagc actgaccccc ctcaccatga ccatcatgat gagttttgcc ttatgccctg 420
aatcctgatg gtttccctaa agttattacg gaaacagacc cctgctttcg aatttacatg 480
ttcatgatgt gcccttgttg taaaccttta cctgtcactt gttt 524

<210> 311
<211> 523
<212> DNA
<213> Homo sapiens

<400> 311
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atgttccctc cgaagggtcg gacaaggctc cggagccctg tagctgccct ccctaggagc 120
cccgggtctt cactggccga ggtgcccacc ccgcagcatt ctgggagtgg tagttttctt 180
ccttcaggtt cattcctggc tggccagtgc ccaagactgg cgagactacg attcccagac 240
gcccaagcga gtcgccggtc acgtggccgc aaggacgctg ggccggtggg cgggggccgg 300
caggtgctcc gcagccgtct gtgccaccca gagccggcgg gccgctaggt ccccggagac 360
cctgctatgg tgcgtgcggg cgccgtgggg gctcatctcc ccgcgtccgg cttggatatc 420
ttcggggacc tgaagaagat gaacaagcgc cagctctatt accaggtttt aaacttcgcc 480
atgatcgtgt cttctgcact catgatatgg aaaggcttga tcg 523

<210> 312
<211> 524
<212> DNA
<213> Homo sapiens

<400> 312
gaattcggca cgagggtgaa ggtgtgtgtc agcttttgcg tcactcgagc cctgggcgct 60
gcttgctaaa gagccgagca cgcgggtctg tcatcatgtc gcgttacggg cggtacggag 120
gagaaaccaa ggtgtatgtt ggtaacctgg gaactggcgc tggcaaagga gagttagaaa 180
gggctttcag ttattatggt cctttaagaa ctgtatggat tgcgagaaat cctccaggat 240
ttgcctttgt ggaattcgaa gatcctagag atgcagaaga tgcagtacga ggactggatg 300
gaaaggtgat ttgtggctcc cgagtgaggg ttgaactatc gacaggcatg cctcggagat 360
cacgttttga tagaccacct gcccgacgtc cctttgatcc aaatgataga tgctatgagt 420
gtggcgaaaa gggacattat gcttatgatt gtcatcgtta cagccggcga agaagaagca 480
ggtcacggtc tagatcacat tctcgatcca gaggaaggcg atac 524

<210> 313
<211> 523

<212> DNA
<213> Homo sapiens

<400> 313
gaattcggca cgaggggtaa caccagaata tttggcaaag ggagaaaaaa aaagcagcga 60
ggcttcgcct tccccctctc ccttttttt tcctcctctt ccttcctcct ccagccgccg 120
ccgaatcatg tcgatgagtc caaagcacac gactccgttc tcagtgtctg acatcttgag 180
tcccctggag gaaagctaca agaaagtggg catggagggc ggcggcctcg gggctccgct 240
ggcggcgtac aggcagggcc aggcggcacc gccaacagcg gccatgcagc agcacgccgt 300
ggggcaccac ggcgccgtca ccgccgccta ccacatgacg gcggcggggg tgccccagct 360
ctcgcactcc gccgtggggg gctactgcaa cggcaacctg ggcaacatga gcgagctgcc 420
gccgtaccag gacaccatga ggaacagcgc ctctggcccc ggatggtacg gcgccaaccc 480
agacccgcgc ttccccgcca gttcttttc ttcaggatca ggc 523

<210> 314
<211> 525
<212> DNA
<213> Homo sapiens

<400> 314
gaattcggca cgagggaaaa ccagagatag agggaaagcc agagagtgaa ggagagccag 60
ggagtgaaac aagggctgca ggaaagcgcc cagctgagga tgatgtaccc aggaaagcca 120
aaagaaaaac taataagggg ctggctcatt acctcaagga gtataaagag gccatacatg 180
atatgaattt cagcaatgag gacatgataa gagaatttga caatatggct aaggtgcagg 240
atgagaagag aaaaagcaaa cagaaattgg gggcgttttt gtggatgcaa agaaatttac 300
aggacccctt ctaccctaga ggtccaaggg aattcagggg tggctgcagg gccccacgaa 360
gggacattga agacattcct tatgtgtagt gtccctggca ggcatttacc aggccatgtg 420
ctttaacgtt cggtaatact ttactttagg catccctcct gttgctagca gccttttgac 480
ctatctgcaa tgcagtgttc tcagtaggaa atgttcatct gttac 525

<210> 315
<211> 358
<212> DNA
<213> Homo sapiens

<400> 315
gaattcggca cgaggggtg gtggagcgct gggcggccag gctccctggc tggccggttt 60
gggcgtctgg gccgtgaagg tgggacctcc tgttccgggc cgcaagtttc cctctccagc 120
cgcccgccgt tcgtagcatg tcccccagaa ctcggggagc gcaggcagga caggcttaga 180
gaagacgcgg tccccagcgc ttgggccacg gacgtcccac cccgctcctc tgtcgctgga 240
gaaccgccgg gccgagccac tgggagaagc aggccagagc cttccagggc ctccggcccg 300
tggacccgag gaggatgagc tggctttttc ccctgaccaa gagcgcctcc tcctccgc 358

<210> 316
<211> 420
<212> DNA
<213> Homo sapiens

<400> 316
gaattcggca cgaggcgttc cttcgcacac tgtgattttg ccctcctgcc cacgcagacc 60
tgcagcgggc aaagagctcc cgaggaagca cagcttgggt caggttcttg cctttcttaa 120
ttttagggac agctaccgga aggaggggaa caaggagttc tcttccgcag ccccttccc 180
cacgcccacc cccagtctcc agggaccctt gcctgcctcc taggctggaa gccatggtcc 240
cgaagtgtag ggcaagggtg cctcaggacc ttttggtctt cagcctccct cagcccccag 300
gatctgggtt aggtggccgt cctcctgctc ctcatgggaa gatgtctcag agccttcatg 360
acctcccctc cccaacccaa tgccaaagtg gacttgggag ctgcacaaag tcagcaggga 420

<210> 317
<211> 518

<212> DNA
<213> Homo sapiens

<400> 317
gaattcggca cgagggctgc cggagggtcg ttttaaaggg cccgcgcgtt gccgcccccc 60
cggcccgcca tgctgctatc cgtgccgctg ctgctcggcc tcctcggcct ggccgtcgcc 120
gagcctgccg tctacttcaa ggagcagttt ctggacggag acgggtggac ttcccgctgg 180
atcgaatcca aacacaagtc agattttggc aaattcgttc tcagttccgg caagttctac 240
ggtgacgagg agaaagataa aggtttgcag acaagccagg atgcacgctt ttatgctctg 300
tcggccagtt tcgagccttt cagcaacaaa ggccagacgc tggtggtgca gttcacggtg 360
aaacatgagc agaacatcga ctgtgggggc ggctatgtga agctgtttcc taatagtttg 420
gaccagacag acatgcacgg agactcagaa tacaacatca tgtttggtcc cgacatctgt 480
ggcctgcacc aaaaagggtc atgtcatctt caactaca 518

<210> 318
<211> 401
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(401)
<223> n = A,T,C or G

<400> 318
aacaccaagg tggacaagag agttgagtcc aaatatggtc ccccatgccc atcatgccca 60
gcacctgagt tcctgggggg accatcagtc ttcctgttcc ccccaaaacc caaggacact 120
ctcatgatct cccggacccc tgaggtcacg tgcgtggtgg tggacgtgag ccaggaagac 180
cccgaggtcc agttcaactg gtacgtggat ggcgtggagg tgcataatgc caagacaaag 240
ccgcgggagg agcagttcaa cagcacgtac cgtgtggtca gcgtcctcac cgtcctgcac 300
caggactggc tgaacggcaa ggagtacaag tgcaaggtct ccaacaaagg cctcccgtcc 360
tccatcgaga aaaccatntn caaagccaaa gggcagcccc g 401

<210> 319
<211> 401
<212> DNA
<213> Homo sapiens

<400> 319
accgtgtact attagccatg gtcaacccca ccgtgttctt cgacattgcc gtcgacggcg 60
agcccttggg ccgcgtctcc tttgagctgt ttgcagacaa ggtcccaaag acagcagaaa 120
attttcgtgc tctgagcact ggagagaaag gatttggtta taagggttcc tgctttcaca 180
gaattattcc agggtttatg tgtcagggtg gtgacttcac acgccataat ggcactggtg 240
gcaagtccat ctatggggag aaatttgaag atgagaactt catcctaaag catacgggtc 300
ctgcatcttg tccatggcaa atgctggacc caacacaaat ggttcccagt ttttcatctg 360
cactgccaag actgagtggt tggatggcaa gcatgtggtg t 401

<210> 320
<211> 471
<212> DNA
<213> Homo sapiens

<400> 320
tagagtccca caaacccttg gcatgcctta atgtttgaga attccattct atttctcatt 60
aatctcttga aagcaaagat attttataaa tctttttgga ccagtgtttt agatggtagt 120
ggctgtggca gtgactttta attagccatc ctgaacccat catttaaaat atttattttt 180
gctttcagaa attttgaaat aagtaaggga aaaaaccaaa ttatttacag atacacataa 240
ccaacccaaa ataaaagcaa aatactaaat taggcacaca gaaagactaa aagtaaattc 300

actaggaaag acactcctca aagatagaat gtaaattttg tgaatccaga gtgctcaaac 360
cagaataacg cttgtcctta taccctaaag gacttgccaa gaaagataaa aagtatttta 420
ttatcccaga aagaatgcaa gggtcttcat ttcagttggc ttataacacc a 471

<210> 321
<211> 471
<212> DNA
<213> Homo sapiens

<400> 321
attactcaac agatttggac acaacggaaa gacaacagtt gatatttcta cttggtgtga 60
gcagtttgca acttttgtt cagagcaact ggacggggcc ccctgttgac ttacaccctc 120
aggacttttt gtcatctgtt ttgttccagc aattcagtga ggttaaagga ctggatgcat 180
ttgttctgag cctgctcact ctagatggtg aatcaatcta cagcctgacc tcgaagccta 240
tactactgtt attagcacgc attatcctag tgaatgtaag acataaactg acagctattc 300
agagcttgcc atggtggact ttgagatgtg tgaatattca tcagcatttg cttgaggaac 360
gctcacctct gctttttact cttgccgaaa actgtattga tcaagtgatg aaactacaga 420
atctgtttgt agatgattca ggtcgatatt tggctattca attccatctg g 471

<210> 322
<211> 601
<212> DNA
<213> Homo sapiens

<400> 322
tgaaggagca gttgccgccg ttggcggcgg cccgagcagt tttcgctgct gctacggctg 60
ttgccatgag gcgaggctag ggaggacctc acttccccgg ggtgtaataa tgttaactga 120
ggccagtcta tccatatggg gatggggaag ccttggcatt gtccttttc tgataacctt 180
tggacccttt gtaatatttt atttgacatt ttatatcctc tgctttgtgg gtgggggttt 240
agtggttact ctcctgtttg gaaaaacaaa ctcagagaag tacctagaac agtgtgaaca 300
ctcatttctt cctccaacat cacctggggt tcctaagtgc ttagaagaaa tgaaacggga 360
agccaggact attaagattg atagaagatt gacgggtgcc aatataattg atgaacctct 420
ccagcaagtt atccagtttt ccttgaggga ttatgtccag tattggtatt atacactaag 480
cgatgatgaa tcttttcttc ttgaaattag gcagactctt caaaacgcac tcattcagtt 540
tgctactagg tcaaaagaaa tagactggca accttatttt actacacgca ttgtagatga 600
c 601

<210> 323
<211> 601
<212> DNA
<213> Homo sapiens

<400> 323
gatgaggtag cagaggctca acgggcagag tttagccctg cccagttctc tggtcctaag 60
aagatcaacc tgaaccactt gttgaatttc acttttgaac cccgtggcca gacgggtcac 120
tttgaaggca gtggacatgg tagctgggga aagaggaaca agtggggaca taagcctttt 180
aacaaggaac tctttttaca ggccaactgc caatttgtgg tgtctgaaga ccaagactac 240
acagctcatt ttgctgatcc tgatacatta gttaactggg actttgtgga acaagtgcgc 300
atttgtagcc atgaagtgcc atcttgccca atatgcctct atccacctac tgcagccaag 360
ataacccgtt gtggacacat cttctgctgg gcatgcatcc tgcactatct ttcactgagt 420
gagaagacgt ggagtaaatg tcccatctgt tacagttctg tgcataagaa ggatctcaag 480
agtgttgttg ccacagagtc acatcagtat gttgttggtg ataccattac gatgcagctg 540
atgaagaagg agaaaggggt ggtggtggct ttgcccaaat ccaaatggat gaatgtagac 600
c 601

<210> 324
<211> 461
<212> DNA
<213> Homo sapiens

<400> 324
catcttcttc ctttcgcggg gtcctccgta gttctggcac gagccaggcg tactgacagg 60
tggaccagcg gactggtgga gatggcgacg ctctctctga ccgtgaattc aggagaccct 120
ccgctaggag ctttgctggc agtagaacac gtgaaagacg atgtcagcat ttccgttgaa 180
gaagggaaag agaatattct tcatgtttct gaaaatgtga tattcacaga tgtgaattct 240
atacttcgct acttggctag agttgcaact acagctgggt tatatggctc taatctgatg 300
gaacatactg agattgatca cttggttgga gttcagtgct acaaaattat cttcatgtga 360
ttcctttact tctacaatta atgaactcaa tcattgcctg tctctgagaa catacttagt 420
tggaaactcc ttgagtttag cagatttatg tgtttgggcc a 461

<210> 325
<211> 461
<212> DNA
<213> Homo sapiens

<400> 325
tcacttttga accccgtggc cagacgggtc actttgaagg cagtggacat ggtagctggg 60
gaaagaggaa caagtgggga cataagcctt ttaacaagga actcttttta caggccaact 120
gccaatttgt ggtgtctgaa gaccaagact acacagctca ttttgctgat cctgatacat 180
tagttaactg ggactttgtg gaacaagtgc gcatttgtag ccatgaagtg ccatcttgcc 240
caatatgcct ctatccacct actgcagcca agataacccg ttgtggacac atcttctgct 300
gggcatgcat cctgcactat ctttcactga gtgagaagac gtggagtaaa tgtcccatct 360
gttacagttc tgtgcataag aaggatctca agagtgttgt tgccacagag tcacatcagt 420
atgttgttgg tgataccatt acgatgcagc tgatgaagaa g 461

<210> 326
<211> 451
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(451)
<223> n = A,T,C or G

<400> 326
ctgtggaggc cagttctgga gctattgcag cctcggttgc ccggccgggg acccgagccg 60
aaaagttatc gtcagaatgt cgggcaaaga ccgaattgaa atctttccct cgcgaatggc 120
acagaccatc atgaangctc gtttaaaggg agcacagaca ggtcgaaacc tcctgaagaa 180
aaaatctgat gccttaactc ttcgatttcg acagatccta aagaagataa tagagactaa 240
aatgttgatg ggcgaagtga tgagagaagc tgccttttca ctagctgaag ccaagttcac 300
agcaggtgac ttcagcacta cagttatcca aaatgtcaat aaagcgcaag tgaagattcg 360
agcgaagaaa gataatgtag caggtgttac tttgccagta tttgaacatt accatgaagg 420
aactgacagt tatgaactga ctggtttagc c 451

<210> 327
<211> 601
<212> DNA
<213> Homo sapiens

<400> 327
gaggggaggc cagcgaagcc gagtaaaacc gccgcccggg agaagactga aggagcagtt 60
gccgccgttg gcggcggccc gagcagtttt cgctgctgct acggctgttg ccatgaggcg 120
aggctaggga ggacctcact tccccggggt gtaataatgt taactgaggc cagtctatcc 180
atatggggat ggggaagcct tggcattgtc ctttttctga taacctttgg acccctttgta 240
atattttatt tgacatttta tatcctctgc tttgtgggtg ggggtttagt ggttactctc 300
ctgtttggaa aaacaaactc agagaagtac ctagaacagt gtgaacactc atttcttcct 360
ccaacatcac ctggggttcc taagtgctta gaagaaatga aacgggaagc caggactatt 420

aagattgata gaagattgac gggtgccaat ataattgatg aacctctcca gcaagttatc 480
cagttttcct tgagggatta tgtccagtat tggtattata cactaagcga tgatgaatct 540
tttcttcttg aaattaggca gactcttcaa aacgcactca ttcagtttgc tactaggtca 600
a 601

<210> 328
<211> 601
<212> DNA
<213> Homo sapiens

<400> 328
ccggaatgat caccaagaca cacaaagtag accttgggct cccagagaag aaaaagaaga 60
agaaagtggt caaagaacca gagactcgat actcagtttt aaacaatgat gattactttg 120
ctgatgtttc tcctttaaga gctacatccc cctctaagag tgtggcccat gggcaggcac 180
ctgagatgcc tctagtgaag aaaaagaaga agaaaaagaa gggtgtcagc acccttgcg 240
aggagcatgt agaacctgag accacgctgc ctgctagacg gacagagaag tcacccagcc 300
tcaggaagca ggtgtttggc cacttggagt tcctcagtgg ggaaaagaaa aataagaagt 360
cacctctagc catgtcccat gcctctgggg tgaaaacctc cccagaccct agacagggtg 420
aggaggaaac cagagttggc aagaagctca aaaaacacaa gaaggaaaaa aaggggggcc 480
aggaccccac agccttctcg gtccaggacc cttggttctg tgaggccagg gaggccaggg 540
atgttgggga cacttgctca gtggggaaga aggatgagga acaggcagcc ttggggcaga 600
a 601

<210> 329
<211> 501
<212> DNA
<213> Homo sapiens

<400> 329
agcagctttc gctccaagct gcatcttgta gacctcgctg gatcagaaag acagaagaaa 60
accaaggctg aaggggatcg tctaaaagag ggtattaata ttaaccgagg cctcctatgc 120
ttgggaaatg taatcagtgc tcttggagat gacaaaaagg gtggctttgt gccctacaga 180
gattccaagt tgactcgact gcttcaagat tctctaggag gtaatagcca tactcttatg 240
atagcctgtg tgagtcctgc tgactccaat ctagaggaaa cattaaatac ccttcgctat 300
gctgacagag caagaaaaat caagaacaaa cctattgtta atattgatcc ccagacagct 360
gaacttaatc atctaaagca acaggtacaa cagctacaag tcttgttgct acaggcccat 420
ggaggtaccc tgcctggatc tataactgtg gaaccatcag agaatctaca atccctgatg 480
gagaagaatc agtccctggt a 501

<210> 330
<211> 451
<212> DNA
<213> Homo sapiens

<400> 330
cgcgaggcgc gcgccatgga acagcggtta gctgagtttc gggcggcgcg gaaacgggcg 60
ggtctggcgg cccaaccccc tgctgccagt cagggcgcac aaaccccagg agagaaggcg 120
gaagcagcag cgactctaaa ggcagcccca ggctggctaa agcggttcct ggtatggaaa 180
cctaggcccg cgagtgcccg ggcccagccc ggcctagttc aggaagcggc tcagccccag 240
ggcagcacat cagagacacc atggaacaca gccattcctc tgccgtcgtg ctgggaccag 300
tctttcctga ccaatatcac cttcttgaag gttcttctct ggttggtcct gctgggactg 360
tttgtggaac tggaatttgg cctgcatatt ttgtcctgtc cttgttctat tggatgtacg 420
tcgggacacg aggccctgaa gagaagaaag a 451

<210> 331
<211> 331
<212> DNA
<213> Homo sapiens

<400> 331
cgttggtcct gtgcggtcac ttagccaaga tgcctgagga aacccagacc caagaccaac 60
cgatggagga ggaggaggtt gagacgttcg cctttcaggc agaaattgcc cagttgatgt 120
cattgatcat caatactttc tactcgaaca aagagatctt tctgagagag ctcatttcaa 180
attcatcaga tgcattggac aaaatcccgt atgaaagctt ggacagaatc caataaatta 240
aaacttcttg ggaaaagaag cttgcattat taacccttta taccgaacca aaccaaagaa 300
tccgaaactt cttcacttat ttggtgggga a 331

<210> 332
<211> 401
<212> DNA
<213> Homo sapiens

<400> 332
tccttcttga tcctgaactg ggttaggtgc cgctgttgct gctcgtgttg aatctagaac 60
cgtagccaga catgggactg gaggacgagc aaaagatgct taccgaatcc ggagatcctg 120
aggaggagga agaggaagag gaggaattag tggatcccct aacaacagtg agagagcaat 180
gcgagcagtt ggagaaatgt gtaaaggccc gggagcggct agagctctgt gatgagcgtg 240
tatcctctcg atcacataca gaagaggatt gcacggagga gctctttgac ttcttgcatg 300
cgagggacca ttgcgtggcc cacaaactct ttaacaactt gaaataaatg tgtggactta 360
attcacccca gtcttcatca tctgggcatc agaatatttc c 401

<210> 333
<211> 331
<212> DNA
<213> Homo sapiens

<400> 333
gatccctgca gaggcctcat cccccgacag cgagccagtc ctagagaagg atgacctcat 60
ggacatggat gcctctcagc agaatttatt tgacaacaag tttgatgaca tctttggcag 120
ttcattcagc agtgatccct tcaatttcaa cagtcaaaat ggtgtgaaca aggatgagaa 180
ggaccactta attgagcgac tatacagaga gatcagtgga ttgaaggcac agctagaaaa 240
catgaagact gagagccagc gggttgtgct gcagctgaag ggccacgtca gcgagctgga 300
agcagatctg gccgagcagc agcacctgcg g 331

<210> 334
<211> 551
<212> DNA
<213> Homo sapiens

<400> 334
agcgggactg gctgggtcgg ctgggctgct ggtgcgagga gccgcggggc tgtgctcggc 60
ggccaagggg acagcgcgtg ggtggccgag gatgctgcgg ggcggtagct ccggcgcccc 120
tagctggtga ctgctgcgcc gtgcctcaca cagccgaggc gggctcggcg cacagtcgct 180
gctccgcgcg cgcgcccggc ggcgctccag gtgctgacag cgcgagagag cgcggccctc 240
aggagcaagg cgaatgtatg acaacatgtc cacaatggtg tacataaagg aagacaagtt 300
ggagaagctt acacaggatg aaattatttc taagacaaag caagtaattc aggggctgga 360
agctttgaag aatgagcaca attccatttt acaaagtttg ctggagacac tgaagtgttt 420
gaagaaagat gatgaaagta atttggtgga ggagaaatca aacatgatcc cggaagtcac 480
tggagatgtt ggagctcggc ctgagtgagg cacaggttat gatggctttg tcaaatcacc 540
tgaatgcttg t 551

<210> 335
<211> 501
<212> DNA
<213> Homo sapiens

<400> 335
caggcggccg agcgggactg gctgggtcgg ctgggctgct ggtgcgagga gccgcggggc 60

tgtgctcggc ggccaagggg acagcgcgtg ggtggccgag gatgctgcgg ggcggtagct 120
ccggcgcccc tagctggtga ctgctgcgcc gtgcctcaca cagccgaggc gggctcggcg 180
cacagtcgct gctccgcgcg cgcgcccggc ggcgctccag gtgctgacag cgcgagagag 240
cgcggccctc aggagcaagg cgaatgtatg acaacatgtc cacaatggtg tacataaagg 300
aagacaagtt ggagaagctt acacaggatg aaattatttc taagacaaag caagtaattc 360
aggggctgga agctttgaag aatgagcaca attccatttt acaaagtttg ctggagacac 420
tgaagtgttt gaagaaagat gatgaaagta atttggtgga ggagaaatca aacatgatcc 480
ggaagtcact ggagatgttg g 501

<210> 336
<211> 521
<212> DNA
<213> Homo sapiens

<400> 336
cctcggcggc ggcggcggtg cttacagcct gagaagagcg tctcgcccgg gagcggcggc 60
ggccatcgag acccacccaa ggcgcgtccc cctcggcctc ccagcgctcc caagccgcag 120
cggccgcgcc ccttcagcta gctcgctcgc tcgctctgct tccctgctgc cggctgcgcc 180
atggcgttgg cgttggcggc gctggcggcg gtcgagccgg cctgcggcag ccggtaccag 240
cagttgcaga atgaagaaga gtctggagaa cctgaacagg ctgcaggtga tgctcctcca 300
ccttacagca gcatttctgc agagagcgca gcatattttg actacaagga tgagtctggg 360
tttccaaagc ccccatctta caatgtagct acaacactgc ccagttatga tgaagcggag 420
aggaccaagg ctgaagctac tatccctttg gttcctggga gagatgagga ttttgtgggt 480
cgggatgatt ttgatgatgc tgaccagctg aggataggaa a 521

<210> 337
<211> 521
<212> DNA
<213> Homo sapiens

<400> 337
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gggtcccaga caaggatcaa gagaacggga ttggcctcca gaggcagagg ttccaaatgg 120
gagtgggctt cctcctagaa agactttctg gaggagaccc ccctactgtg taacagagga 180
ggactttggg attaagaaaa gcattccagg aagccgacag tgtcagcaaa cgtggaggtg 240
agatccttca aagtgagtgg tgtggaggtt tccagaattt tctgagcctg aagggaaggt 300
tggagagcag accctgccct ttggaggctt gacttagccc tgagggcacc ctgtagccag 360
ggtgggcaga tgccaatatg gtagagacga agactgagta gggagccagc cacagtgctt 420
gtggtctcag gcagggagtg aagaccagag tggagcaggc tagaaacctg ggaaggaagc 480
aggttcccca gtataagccc atgatgtgtg aagaatgagc c 521

<210> 338
<211> 581
<212> DNA
<213> Homo sapiens

<400> 338
atactgcttg cttggagatg tcctcggaga ccattcttgc tatgacaagg cctgggagtt 60
gtcccggtac cgcagtgctc gtgctcagcg ctccaaagcc ctccttcatc ttcggaacaa 120
ggagtttcaa gagtgtgtag agtgcttcga acgctcggtt aagattaatc ccatgcagct 180
cggggtgtgg ttttctctcg gttgtgccta tttggccttg gaagactatc aaggttcagc 240
aaaggcattt cagcgctgtg tgactctaga acccgataat gctgaagctt ggaacaattt 300
gtcaacttcc tatatccgat taaaacaaaa agtaaaagct tttagaactt tacaagaagc 360
tctcaagtgt aactatgaac actggcagat ttgggaaaac tacatcctca ccagcactga 420
cgttggggaa ttttcagaag ccattaaagc ttatcaccgg ctcttggact tacgtgacaa 480
atacaaagat gttcaggtcc ttaaaattct agtcagggca gtgattgatg ggatgactga 540
tcgaagtgga gatgttgcaa ctggcctcaa aggaaagctg c 581

<210> 339

<211> 581
<212> DNA
<213> Homo sapiens

<400> 339
aagaagaaga agctcgcgtt cgtgaagaag cagagagggt ccggcaggaa cgagagaagc 60
atttccagag agaagagcaa gagcgcctgg agagaaagaa gcgacttgag gagattatga 120
aaagaaccag gagaacagaa gctacagata agaaaaccag tgatcagaga aacggtgata 180
tagccaaggg agctctcact ggaggaacag aggtgtctgc acttccatgt acaacaaacg 240
ctccgggaaa tggaaagcca gttggcagcc cacatgtggt tacctcacac cagtcaaaag 300
aaaaaaaaaa gcgtgatgga atagctattg gatcaggtta caaaaaacaa tttttaaaaa 360
taagctaaca tctaagaaac atcattttgc ctatactgcc tcccccaaaa tcctgttttt 420
actcagtgaa cacctaagcc cactcagaaa tgttctggat tgtcattttc tccatccttt 480
agcaccttct tattttgggg ggagctctga agccttgcaa gaagtgggag agaaaaggac 540
caggtgtgac agaagggacg atttaagtta ttacaataaa c 581

<210> 340
<211> 571
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(571)
<223> n = A,T,C or G

<400> 340
ggtggcaaat tcaagtcctg ttaaccccgt ggtgttcttt gatgtcagta ttggcggtca 60
ggaagttggc cgcatgaaga tcgagctctt tgcagacgtt gtgcctaaga cggccgagaa 120
ctttaggcag ttctgcaccg gagaattcag gaaagatggg gttccaatag gatacaaagg 180
aagcaccttc cacagggtca taaaggattt catgattcag ggtggagatt ttgttaatgg 240
agatggtact ggagtcgcca gtatttaccg ggggccattt gcagatgaaa attttaaact 300
tagacactca gctccaggcc tgctttccat ggcgaacagt ggtccaagta caaatggctg 360
tcagttcttt atcacctgct ctaagtgcga ttggctggat gggaagcatg tggtgtttgg 420
aaaaatcatc gatggacttc tagtgatgag aaagattgag aatgttccca caggccccaa 480
caataagccc aagctacctg tggtgatctc cagtgtgggg agatgtagtc cagacaaaga 540
ctgaatcagt atacttgctc gacttcaagg n 571

<210> 341
<211> 581
<212> DNA
<213> Homo sapiens

<400> 341
taatgagacc aaagtttgca agggcaggac gagcccgtgc taacagagaa agtgttgttt 60
cctcaatttg gttttagact gtcttgtcct atgggggaga aaagatctgc ccttgggaga 120
ggtgccaact ttatagatct attaataaaa gaactggcag gcttacagtt cttgccaatg 180
aggaaacttg aatgagagaa gccaggctca accttggcca acagactgga gcccatcacc 240
ctaacttcac cccgcttctc cttacccaac cgtcaaaggc taggcagcac ccacccagca 300
gcttccacct ggctgaagcc tgcacctgct tcagaccaag ggttagatgg aaatttggca 360
tgggaagaga gggctcacct gtgggcagga tagactctat ccaagaagga gaactgaaaa 420
atgaaaacct atgagacaag gggtgatcct gaagcaggca ggagaaaggg ctggagggag 480
aggcactggg gaatttttcc tggtgaatac tgaagttact agatgttttg tcttgcaaaa 540
ctcaagggaa aactctcaaa ctctaatggt tggcctattc t 581

<210> 342
<211> 451
<212> DNA
<213> Homo sapiens

<400> 342
gcagaccaga cttcgctcgt actcgtgcgc ctcgcttcgc ttttcctccg caaccatgtc 60
tgacaaaccc gatatggctg agatcgagaa attcgataag tcgaaactga agaagacaga 120
gacgcaagag aaaaatccac tgccttccaa agaaacgatt gaacaggaga agcaagcagg 180
cgaatcgtaa tgaggcgtgc gccgccaata tgcactgtac attccacaag cattgccttc 240
ttattttact tcttttagct gtttaacttt gtaagatgca aagaggttgg atcaagttta 300
aatgactgtg ctgccccttt cacatcaaag aactactgac aacgaagccg cgcctgcctt 360
tcccatctgt ctatctatct ggctggcagg gaaggaaaga acttgcattg ttggtgaagg 420
aagaagtggg gggtggaaga aatgggggtg g 451

<210> 343
<211> 601
<212> DNA
<213> Homo sapiens

<400> 343
tgacctcatg gacatggatg cctctcagca gaatttattt gacaacaagt ttgatgacat 60
ctttggcagt tcattcagca gtgatccctt caatttcaac agtcaaaatg gtgtgaacaa 120
ggatgagaag gaccacttaa ttgagcgact atacagagag atcagtggat tgaaggcaca 180
gctagaaaac atgaagactg agagccagcg ggttgtgctg cagctgaagg gccacgtcag 240
cgagctggaa gcagatctgg ccgagcagca gcacctgcgg cagcaggcgg ccgacgactg 300
tgaattcctg cgggcagaac tggacgagct caggaggcag cgggaggaca ccgagaaggc 360
tcagcggagc ctgtctgaga tagaaaggaa agctcaagcc aatgaacagc gatatagcaa 420
gctaaaggag aagtacagcg agctggttca gaaccacgct gacctgctgc ggaagaatgc 480
agaggtgacc aaacaggtgt ccatggccag acaagcccag gtagatttgg aacgagagaa 540
aaaagagctg gagggattcg ttggagccgc tcagtgaccc agggccagcg ggaagactca 600
a 601

<210> 344
<211> 571
<212> DNA
<213> Homo sapiens

<400> 344
gcgacccggg gagcgagcac gtcgctccgc accgctcttc ctccagccgc tgagccgtcc 60
cttctcgcca tgtcccagag caggcaccgc gccgaggccc cgccgctgga gcgcgaggac 120
agtgggacct tcagtttggg gaagatgata acagctaagc cagggaaaac accgattcag 180
gtattacacg aatacggcat gaagaccaag aacatcccag tttatgaatg tgaaagatct 240
gatgtgcaaa tacacgtgcc cactttcacc ttcagagtaa ccgttggtga cataacctgc 300
acaggtgaag gtacaagtaa gaagctggcg aaacatagag ctgcagaggc tgccataaac 360
attttgaaag ccaatgcaag tatttgcttt gcagttcctg acccttaat gcctgaccct 420
tccaagcaac caaagaacca gcttaatcct attggttcat tacaggaatt ggctattcat 480
catggctgga gacttcctga atataccctt tcccaggaag gaggacctgc tcataagaga 540
gaatatacta caatttgcag gctagagtca t 571

<210> 345
<211> 551
<212> DNA
<213> Homo sapiens

<400> 345
gacctggcgc tttgtgcggc tccaggcctc cgagtggact ccagaaagcc tgaaaagcta 60
tcatggcagc aaggcccaag ctccactatc ccaacggaag aggccggatg gagtccgtga 120
gatgggtttt agctgccgcc ggagtcgagt ttgatgaaga atttctggaa acaaaagaac 180
agttgtacaa gttgcaggat ggtaaccacc tgctgttcca acaagtgccc atggttgaaa 240
ttgacgggat gaagttggta cagacccgaa gcattctcca ctacatagca gacaagcaca 300
atctctttgg caagaacctc aaggagagaa ccctgtactg tggcccctct cgagtgttgt 360
cacttgtcag cttactgatg ccttagctga ttagcaacct ctgtagcaca ccacatttac 420

tttatgtctt acatagttag tgagatcagg gaacaaaaac ccaagaaggt cacgaagacc 480
agttggaact tcagtagaga gagtctgagt aaaacaaaag aatagggatt cagatattga 540
atactatatc t 551

<210> 346
<211> 501
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(501)
<223> n = A,T,C or G

<400> 346
tatgggaaac tgctctttat ttagaccttt gggacaaaat taactttggt cacatattac 60
ttaaaaaaaa atccagtttt acatatttct aaatagatag aactaaatga tcagagaatt 120
tcttctgtaa aaattggcca aattttatca aaaatctaac atacgataca atccaaatta 180
taaaaagact acttgggatc ataatattcc aaatgtatga cagttataac tccatcttaa 240
caagngtgaa aagtacttgc tctcatgttg ctttggtcca aaagagtaga gctaactcag 300
taacaggcaa ctaagtaccc aatcttttgc caaaattaat ttanattgtg actggcagca 360
gaaatatcca taatgaacag ctctactata acaaagaata attaaagaat acttttcgtg 420
aacatatcac agtatcaaat acatttttat aagagaaaaa tatgaaggaa atgataaaat 480
agctatcaca aacaaaaaga a 501

<210> 347
<211> 621
<212> DNA
<213> Homo sapiens

<400> 347
gcccgggaga agactgaagg agcagttgcc gccgttggcg gcggcccgag cagttttcgc 60
tgctgctacg gctgttgcca tgaggcgagg ctagggagga cctcacttcc ccggggtgta 120
ataatgttaa ctgaggccag tctatccata tggggatggg gaagccttgg cattgtcctt 180
tttctgataa cctttggacc ctttgtaata ttttatttga cattttatat cctctgcttt 240
gtgggtgggg gtttagtggt tactctcctg tttggaaaaa caaactcaga gaagtaccta 300
gaacagtgtg aacactcatt tcttcctcca acatcacctg gggttcctaa gtgcttagaa 360
gaaatgaaac gggaagccag gactattaag attgatagaa gattgacggg tgccaatata 420
attgatgaac ctctccagca agttatccag ttttccttga gggattatgt ccagtattgg 480
tattatacac taagcgatga tgaatctttt cttcttgaaa ttaggcagac tcttcaaaac 540
gcactcattc agtttgctac taggtcaaaa gaaatagact ggcaacctta ttttactacc 600
cgcattgtag atgactttgg c 621

<210> 348
<211> 511
<212> DNA
<213> Homo sapiens

<400> 348
cggcggccgg cgggcggcga tggcggcggc ggaggccggt ggcgacgacg cccgctgcgt 60
gcggctgagc gccgagcggg.cacaggcgct gctggccgac gtggacacgc tgctgttcga 120
ctgcgacggc gtgctgtggc gcggggagac cgccgtgcct ggcgcgcccg aggccctgcg 180
ggcgctgcga gcccgcggca agcgcctggg cttcatcacc aacaacagca gcaagacccg 240
cgctgcctac gccgagaagc tgcggcgcct gggcttcggc ggccccgcgg ggcccggcgc 300
cagcctggag gtcttcggca cggcctactg caccgcgctc tacctgcgcc agcgcctggc 360
cggcgccccc gcgcccaagg cctacgtgct gggcagccca gccctggccg cggagctgga 420
gccgtgggcg tcgccagcgt gggcgtgggg cccgaccact gcagggcgag ggtcccggcg 480
actggctgca cgcccgttgg agccgactgc g 511

<210> 349
<211> 521
<212> DNA
<213> Homo sapiens

<400> 349
gctcaggcgc ctgcggctgg gtgagcgcac gcgaggcggc gaggcggcag cgtgtttcta 60
ggtcgtggcg tcgggcttcc ggagctttgg cggcagctag gggaggatgg cggagtcttc 120
ggataagctc tatcgagtcg agtacgccaa gagcgggcgc gcctcttgca agaaatgcag 180
cgagagcatc cccaaggact cgctccggat ggccatcatg gtgcagtcgc ccatgtttga 240
tggaaaagtc ccacactggt accacttctc ctgcttctgg aaggtgggcc actccatccg 300
gcaccctgac gttgaggtgg atgggttctc tgagcttcgg tgggatgacc agcagaaagt 360
caagaagaca gcggaagctg gaggagtgac aggcaaaggc caggatggaa ttggtagcaa 420
ggcagagaag actctgggtg actttgcagc agagtatgcc aagtccaaca gaagtacgtg 480
caaggggtg tatggagaag aatagaaaaa gggccaggtg c 521

<210> 350
<211> 451
<212> DNA
<213> Homo sapiens

<400> 350
gccggcgggc ggcgatggcg gcggcggagg ccggtggcga cgacgcccgc tgcgtgcggc 60
tgagcgccga gcgggcacag gcgctgctgg ccgacgtgga cacgctgctg ttcgactgcg 120
acggcgtgct gtggcgcggg gagaccgccg tgcctggcgc gcccgaggcc ctgcgggcgc 180
tgcgagcccg cggcaagcgc ctgggcttca tcaccaacaa cagcagcaag acccgcgctg 240
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tggaggtctt cggcacggcc tactgcaccg cgctctacct gcgccagcgc ctggccggcg 360
cccccgcgcc caaggcctac gtgctgggca gcccagccct ggccgcggag ctggagccgt 420
gggcgtcgcc agcgtgggcg tggggcccga c 451

<210> 351
<211> 581
<212> DNA
<213> Homo sapiens

<400> 351
agagagagag agagagagag agagagagag agagagacct cgtgccgaat tcggcacgag 60
gcctcgtgcc ggaaacttag tgatggacaa gttggtggtt tcataaatta tcgagatagc 120
aagttaacac gaattctcca gaattccttg ggaggaaatg caaagacacg tattatctgc 180
acaattactc cagtatcttt tgatgaaaca cttactgctc tccagtttgc cagtactgct 240
aaatatatga agaatactcc ttatgttaat gaggtatcaa ctgatgaagc tctcctgaaa 300
aggtatagaa aagaaataat ggatcttaaa aaacaattag aggaggtttc tttagagacg 360
cgggctcagg caatggaaaa agaccaattg gcccactttt ggaagaaaaa gatttgcttc 420
agaaagtaca gaatgagaaa attgaaaact taacacggat gctggtgacc tcttcttccc 480
tcacgttgca ccaggaatta aaggctaaaa gaaaacgaag agttacttgg tgccttgcaa 540
aattaccaaa tgaagaactc aacttttcag atcattttat t 581

<210> 352
<211> 461
<212> DNA
<213> Homo sapiens

<400> 352
aaaggcgatg aggtggatgg agtggatgaa gtggcgaaga agaaatctaa aaaagaaaaa 60
gacaaggata gtaagcttga aaaagcccta aaggctcaga acgacctgat ctggaacatc 120
aaggacgagc taaagaaagt gtgttcaact aatgacctga aggagctact catcttcaac 180
aagcagcaag tgccttctgg ggagtcggcg atcttggacc gagtagctga tggcatggtg 240
ttcggtgccc tccttccctg cgaggaatgc tcgggtcagc tggtcttcaa gagcgatgcc 300

tattactgca ctggggacgt cactgcctgg accaagtgta tggtcaagac acagacaccc 360
aaccggaagg agtgggtaac cccaaaggaa ttccgagaaa tctcttacct caagaaattg 420
aaggttaaaa agcaggaccg tatattcccc ccagaaccag c 461

<210> 353
<211> 491
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(491)
<223> n = A,T,C or G

<400> 353
atggcggcgg cggaggccgg tggcgacgac gcccgctgcg tgcggctgag cgccgagcgg 60
gcacaggcgc tgctggccga cgtggacacg ctgctgttcg actgcgacgg cgtgctgtgg 120
cgcggggaga ccgccgtgcc tggcgcgccc gaggccctgc gggcgctgcg agcccgcggc 180
aagcgcctgg gcttcatcac caacaacagc agcaagaccc gcgctgccta cgccgagaag 240
ctgcggcgcc tgggcttcgg cggccccgcg gggcccggcg ccagcctgga ggtcttcggc 300
acggcctact gcaccgcgct ctacctgcgc cagcgcctgg ccggcgcccc cgcgcccaag 360
gcctacgtgc tgggcaaccc agccctggcc gcgganctgg agccgtgggc gtcgccagcg 420
tgggcgtggg gcccgaccac tgcaagggca gggtcccggc gactggctga cgccccgctg 480
gaacccgact g 491

<210> 354
<211> 401
<212> DNA
<213> Homo sapiens

<400> 354
ggcgtcccgg tgtggctgtg ccgttggtcc tgtgcggtca cttagccaag atgcctgagg 60
aaacccagac ccaagaccaa ccgatggagg aggaggaggt tgagacgttc gcctttcagg 120
cagaaattgc ccagttgatg tcattgatca tcaatacttt ctactcgaac aaagagatct 180
ttctgagaga gctcatttca aattcatcag atgcattgga caaaatccgg tatgaaagct 240
tgacagatcc cagtaaatta gactctggga aagagctgca tattaacctt ataccgaaca 300
aacaagatcg aactctcact attgtggata ctggaattgg aatgaccaag gctgacttga 360
tcaataacct tggtactatc gccaagtctg ggaccaaagc g 401

<210> 355
<211> 451
<212> DNA
<213> Homo sapiens

<400> 355
tcttcagcgc atcagaagta tccagaatgt tcctgaaagc tcaggggctg tggaaactgt 60
tccagcattt caagaaatta cttctatgaa agaacgatgc aacaagcttc ttcagaaagt 120
tcagaaaaat aaagaattgg tgcagactga aatccaagaa agacattcct tcacaaaaga 180
gataattgct ttgaagaatt tctttcaaca gaccacaact tcattccaaa atatggcatt 240
ccaggatcac ccagaaaagt cagaacaatt tgaggagctt caaagcatcc ttaagaaagg 300
gaaactaact tttgagaata ttatggaaaa actgcgaatc aagtattccg aaatgtacac 360
catagtccct gcagagattg aatcccaggt ggaagaatgc agaaaagctt tagaagacat 420
agatgagaag attagccaat gaagtcttaa a 451

<210> 356
<211> 441
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(441)
<223> n = A,T,C or G

<400> 356
gtcgcgcatc cggcggccca tgaacgcctt catggtgtgg gcaaaggacg agcgcaagcg 60
gctggctcag cagaacccgg acctgcacaa cgcggtgctc agcaagatgc tgggcaaagc 120
gtggaaggag ctgaacgcgg cggagaagcg gcccttcgtg gaggaagccg aacggctgcg 180
cgtgcagcac ttgcgcgacc accccaacta caagtaccgg ccgcgccgca agaagcaggc 240
gcgcaaggcc cggcggctgg agcccggctc tgctcccggg attagcgccc ccgcagccac 300
cgccgacctt tcccgcggcg tctggctcgn tcgcgccttc cgcgagctgc cccgctgggc 360
gccgagttca cggctggggc tgccaccccg agcgtcgctc tgacggctga cccgggagct 420
gcttttccac gccgcgcgcc a 441

<210> 357
<211> 451
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(451)
<223> n = A,T,C or G

<400> 357
gcggcggcgg aggccggtgg cgacgacgcc cgctgcgtgc ggctgagcgc cgagcgggca 60
caggcgctgc tggccgacgt ggacacgctg ctgttcgact gcgacggcgt gctgtggcgc 120
ggggagaccg ccgtgcctgg cgcgcccgag gccctgcggg cgctgcgagc ccgcggcaag 180
cgcctgggct tcatcaccaa caacagcagc aagacccgcg ctgcctacgc cgagaagctg 240
cggcgcctgg gcttcggcgg ccccgcgggg cccggcgcca gcctggaggt cttcggcacg 300
gcctactgca ccgcgctcta cctgcgccag cgcctggccg gcgcccccgc gcccaagcct 360
acgtgctggg cagcccagcc ctggccgcgg anctggaagc cgtgggcgtc gccagcgtgg 420
gcgtggggcc cgaaccactt gcagggcgag g 451

<210> 358
<211> 571
<212> DNA
<213> Homo sapiens

<400> 358
gcggcgatgg cggcggcgga ggccggtggc gacgacgccc gctgcgtgcg gctgagcgcc 60
gagcgggcac aggcgctgct ggccgacgtg gacacgctgc tgttcgactg cgacggcgtg 120
ctgtggcgcg gggagaccgc cgtgcctggc gcgcccgagg ccctgcgggc gctgcgagcc 180
cgcggcaagc gcctgggctt catcaccaac aacagcagca agacccgcgc tgcctacgcc 240
gagaagctgc ggcgcctggg cttcggcggc cccgcggggc ccggcgccag cctggaggtc 300
ttcggcacgg cctactgcac cgcgctctac ctgcgccagc gcctggccgg cgcccccgcg 360
cccaagccta cgtgctgggc agcccagccc tggccgcgga gctggaggcc gtgggcgtcg 420
ccagcgtggg cgtggggccc gaccactgca gggcgagggt cccggcgact ggctgcacgc 480
gccgctggag cccgacgtgc gcgcggtggt ggtgggcttt gacccgcact tagctacatg 540
aagctcacca agcccttgcg ctacttgaag a 571

<210> 359
<211> 511
<212> DNA
<213> Homo sapiens

<400> 359
cgctgctgtt atggccgcct ccttgaggta gtatccgcac atggaattct agggccgcag 60

gtgtatttac ggtaactgtc gccactagat ttcagcgcct ttggactctc ctgttttcac 120
tttcttttgt tgactcccgt gtggccctcg tgggagcctg ttttggctgc agcggtgtct 180
ggggtgatgt ggaccccgga gctggcaatt ctgaggggat tccccactga ggctgagcgg 240
cagcaatgga aacaggaggg ggtcgtcggt tcagagagtg gatctttcct acaattgctg 300
ctggaaggga actatgaagc catattctta aattcaatga ctcaaaatat ttttaattca 360
acaacaaccg ctgaagaaaa gattgatagc tacctggaga agcaggtagt aacattcctg 420
gattactcaa cagatttgga cacaacggaa agacaacagt tgatatttct acttggtgtg 480
agcagtttgc aacttttttgt tcaaagcaac t 511

<210> 360
<211> 481
<212> DNA
<213> Homo sapiens

<400> 360
gcgttctcgg ggagctgctg ccgtagctgc cgccgccgct accaccgcgt tcgggtgtag 60
aatttggaat ccctgcgccg cgttaacaat gaagcagagt tcgaacgtgc cggctttcct 120
cagcaagctg tggacgcttg tggaggaaac ccacactaac gagttcatca cctggagcca 180
gaatggccaa agttttctgg tcttggatga gcaacgattt gcaaaagaaa ttcttcccaa 240
atatttcaag cacaataata tggcaagctt tgtgaggcaa ctgaatatgt atggtttccg 300
taaagtagta catatcgact ctggaattgt aaagcaagaa agagatggtc ctgtagaatt 360
tcagcatcct tacttcaaac aaggacagga tgacttgttg gagaacatta aaaggaaggt 420
ttcatcttca aaaccagaag aaaataaaat tcgtcaggaa gatttaacaa aaattataag 480
t 481

<210> 361
<211> 551
<212> DNA
<213> Homo sapiens

<400> 361
cgtagaggaa gacactgtgg aggccagttc tggagctatt gcagcctcgg ttgcccggcc 60
ggggacccga gccgaaaagt tatcgtcaga atgtcgggca aagaccgaat tgaaatcttt 120
ccctcgcgaa tggcacagac catcatgaag gctcgtttaa agggagcaca gacaggtcga 180
aacctcctga agaaaaaatc tgatgcctta actcttcgat ttcgacagat cctaaagaag 240
ataatagaga ctaaaatgtt gatgggcgaa gtgatgagag aagctgcctt ttcactagct 300
gaagccaagt tcacagcagg tgacttcagc actacagtta tccaaaatgt caataaagcg 360
caagtgaaga ttcgagcgaa gaaagataat gtagcaggtg ttactttgcc agtatttgaa 420
cattaccatg aaggaactga cagttatgaa ctgactggtt tagccagagg tggggaacag 480
ttggctaaat taaagaggaa ttatgcccaa agcagtggaa ctactggtgg aactagcttc 540
tcttgcagac t 551

<210> 362
<211> 481
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(481)
<223> n = A,T,C or G

<400> 362
gggttacatt ttggattaaa cctgtttccc ggttatgtgt agggaacagc aaagngatgc 60
acnaactttg aacattcgtt atggggaaaa catcctttaa cttcggggtc gtctgccaaa 120
gcagggtctg ggagggtcca tgcagttccc gntggtgtgg agggaaatgc cctggtctgg 180
cctccgagcc cccaggtcca ccgtctcccc tcccctcatt tgtaanaata gctacacact 240
aacattttgg gaaggagagg cacataactt tttttaacat ttggtaacta ggttatgggc 300
tctacattgt cagctacttg ggatatatat ttaattttct taaattcccg ttaaactcta 360

ttttatggtt ttgatttcag attgcaaaca tgtaaaacct gcatagcagc gagttctcgg 420
ttttgcggtt tctttagttc tttactgtca ctgtcatgta atcagctaat tctcttgtgg 480
a 481

<210> 363
<211> 461
<212> DNA
<213> Homo sapiens

<400> 363
ggaaccagga cctcggcgtg gcctagcgag ttatggcgac gaaggccgtg tgcgtgctga 60
agggcgacgg cccagtgcag ggcatcatca atttcgagca gaaggaaagt aatggaccag 120
tgaaggtgtg gggaagcatt aaaggactga ctgaaggcct gcatggattc catgttcatg 180
agtttggaga taatacagca ggctgtacca gtgcaggtcc tcactttaat cctctatcca 240
gaaaacacgg tgggccaaag gatgaagaga ggcatgttgg agacttgggc aatgtgactg 300
ctgacaaaga tggtgtggcc gatgtgtcta ttgaagattc tgtgatctca ctctcaggag 360
accattgcat cattggccgc acactggtgg tccatgaaaa acagatgact tgggcaaagg 420
tggaaatgaa gaaagtacaa agacaggaaa cgcttgaagt c 461

<210> 364
<211> 531
<212> DNA
<213> Homo sapiens

<400> 364
ggttctactt tctgcacgtc agaaatcaat tccatgtcag ctcgagtcct gctcttgctg 60
gtggtcccag gccatctgat tttcttctac atcatctacc tggtggaggg tcagtcagtc 120
ataaacagcc agacctttgt ggtgctctac ctgctggcag gcctgatcca ggtgacaatc 180
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aaccactgca tcccctacct tacagggctg ggggacctgc tcggtactgg cctcctggca 300
ctctgctttt tcactgactg gctactgaag agcaaggcag agctgggtgg catctcagaa 360
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ctcacatcag tgggatacag aaattcagtt tctcccttgc caggtccttg ggatggttga 480
cccctgcctc tgcagtaacc ttttgtgagt cttgctaagg tagctctcac a 531

<210> 365
<211> 4834
<212> DNA
<213> Homo sapiens

<400> 365
gatgtggagc tggggtccct gcaagtcatg aacaaaacga gaaagattat ggaacatggg 60
ggggccacct tcatcaatgc ctttgtgact acacccatgt gctgcccgtc acggtcctcc 120
atgctcaccg ggaagtatgt gcacaatcac aatgtctaca ccaacaacga gaactgctct 180
tccccctcgt ggcaggccat gcatgagcct cggacttttg ctgtatatct taacaacact 240
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tgtcgcaatg gcatcaaaga aaagcatgga tttgattatg caaaggacta cttcacagac 420
ttaatcacta acgagagcat taattacttc aaaatgtcta agagaatgta tccccatagg 480
cccgttatga tggtgatcag ccacgctgcg ccccacggcc ccgaggactc agccccacag 540
ttttctaaac tgtaccccaa tgcttcccaa cacataactc ctagttataa ctatgcacca 600
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gagaggctgt ataacatgct cgtggagacg ggggagctgg agaatactta catcatttac 780
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ccaggtaaca ggtttcgaac aaacaagaag gccaaaattt ggcgtgatac attcctagtg 1080
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gaatgtagct gcagtaaaca aagctattac aataaagaga aaggtgtaaa aaagcaagag 1920
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caacttttca aggagaacaa ccgtaggagg aagaaggaga ggaaggagaa gagacggcag 2040
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gtttttgctt accctaagag aggttttctt cttattttta gataattcaa gtgcttagat 4500
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tgaataatgt gctttgtaaa aagatttcaa gttattagga agcatactct gttttttaat 4740
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caatatttct tcaaataaaa ggtgtttaaa cttt 4834

<210> 366
<211> 818
<212> PRT
<213> Homo sapiens

<400> 366
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5 10 15
Met Glu His Gly Gly Ala Thr Phe Ile Asn Ala Phe Val Thr Thr Pro
20 25 30
Met Cys Cys Pro Ser Arg Ser Ser Met Leu Thr Gly Lys Tyr Val His
35 40 45
Asn His Asn Val Tyr Thr Asn Asn Glu Asn Cys Ser Ser Pro Ser Trp
50 55 60
Gln Ala Met His Glu Pro Arg Thr Phe Ala Val Tyr Leu Asn Asn Thr
65 70 75 80
Gly Tyr Arg Thr Ala Phe Phe Gly Lys Tyr Leu Asn Glu Tyr Asn Gly
85 90 95
Ser Tyr Ile Pro Pro Gly Trp Arg Glu Trp Leu Gly Leu Ile Lys Asn
100 105 110
Ser Arg Phe Tyr Asn Tyr Thr Val Cys Arg Asn Gly Ile Lys Glu Lys
115 120 125
His Gly Phe Asp Tyr Ala Lys Asp Tyr Phe Thr Asp Leu Ile Thr Asn
130 135 140
Glu Ser Ile Asn Tyr Phe Lys Met Ser Lys Arg Met Tyr Pro His Arg
145 150 155 160
Pro Val Met Met Val Ile Ser His Ala Ala Pro His Gly Pro Glu Asp
165 170 175
Ser Ala Pro Gln Phe Ser Lys Leu Tyr Pro Asn Ala Ser Gln His Ile
180 185 190
Thr Pro Ser Tyr Asn Tyr Ala Pro Asn Met Asp Lys His Trp Ile Met
195 200 205
Gln Tyr Thr Gly Pro Met Leu Pro Ile His Met Glu Phe Thr Asn Ile
210 215 220
Leu Gln Arg Lys Arg Leu Gln Thr Leu Met Ser Val Asp Asp Ser Val
225 230 235 240
Glu Arg Leu Tyr Asn Met Leu Val Glu Thr Gly Glu Leu Glu Asn Thr
245 250 255
Tyr Ile Ile Tyr Thr Ala Asp His Gly Tyr His Ile Gly Gln Phe Gly
260 265 270
Leu Val Lys Gly Lys Ser Met Pro Tyr Asp Phe Asp Ile Arg Val Pro
275 280 285
Phe Phe Ile Arg Gly Pro Ser Val Glu Pro Gly Ser Ile Val Pro Gln
290 295 300
Ile Val Leu Asn Ile Asp Leu Ala Pro Thr Ile Leu Asp Ile Ala Gly
305 310 315 320
Leu Asp Thr Pro Pro Asp Val Asp Gly Lys Ser Val Leu Lys Leu Leu
325 330 335
Asp Pro Glu Lys Pro Gly Asn Arg Phe Arg Thr Asn Lys Lys Ala Lys
340 345 350
Ile Trp Arg Asp Thr Phe Leu Val Glu Arg Gly Lys Phe Leu Arg Lys
355 360 365
Lys Glu Glu Ser Ser Lys Asn Ile Gln Gln Ser Asn His Leu Pro Lys

370 375 380
Tyr Glu Arg Val Lys Glu Leu Cys Gln Gln Ala Arg Tyr Gln Thr Ala
385 390 395 400
Cys Glu Gln Pro Gly Gln Lys Trp Gln Cys Ile Glu Asp Thr Ser Gly
405 410 415
Lys Leu Arg Ile His Lys Cys Lys Gly Pro Ser Asp Leu Leu Thr Val
420 425 430
Arg Gln Ser Thr Arg Asn Leu Tyr Ala Arg Gly Phe His Asp Lys Asp
435 440 445
Lys Glu Cys Ser Cys Arg Glu Ser Gly Tyr Arg Ala Ser Arg Ser Gln
450 455 460
Arg Lys Ser Gln Arg Gln Phe Leu Arg Asn Gln Gly Thr Pro Lys Tyr
465 470 475 480
Lys Pro Arg Phe Val His Thr Arg Gln Thr Arg Ser Leu Ser Val Glu
485 490 495
Phe Glu Gly Glu Ile Tyr Asp Ile Asn Leu Glu Glu Glu Glu Glu Leu
500 505 510
Gln Val Leu Gln Pro Arg Asn Ile Ala Lys Arg His Asp Glu Gly His
515 520 525
Lys Gly Pro Arg Asp Leu Gln Ala Ser Ser Gly Gly Asn Arg Gly Arg
530 535 540
Met Leu Ala Asp Ser Ser Asn Ala Val Gly Pro Pro Thr Thr Val Arg
545 550 555 560
Val Thr His Lys Cys Phe Ile Leu Pro Asn Asp Ser Ile His Cys Glu
565 570 575
Arg Glu Leu Tyr Gln Ser Ala Arg Ala Trp Lys Asp His Lys Ala Tyr
580 585 590
Ile Asp Lys Glu Ile Glu Ala Leu Gln Asp Lys Ile Lys Asn Leu Arg
595 600 605
Glu Val Arg Gly His Leu Lys Arg Arg Lys Pro Glu Glu Cys Ser Cys
610 615 620
Ser Lys Gln Ser Tyr Tyr Asn Lys Glu Lys Gly Val Lys Lys Gln Glu
625 630 635 640
Lys Leu Lys Ser His Leu His Pro Phe Lys Glu Ala Ala Gln Glu Val
645 650 655
Asp Ser Lys Leu Gln Leu Phe Lys Glu Asn Asn Arg Arg Arg Lys Lys
660 665 670
Glu Arg Lys Glu Lys Arg Arg Gln Arg Lys Gly Glu Glu Cys Ser Leu
675 680 685
Pro Gly Leu Thr Cys Phe Thr His Asp Asn Asn His Trp Gln Thr Ala
690 695 700
Pro Phe Trp Asn Leu Gly Ser Phe Cys Ala Cys Thr Ser Ser Asn Asn
705 710 715 720
Asn Thr Tyr Trp Cys Leu Arg Thr Val Asn Glu Thr His Asn Phe Leu
725 730 735
Phe Cys Glu Phe Ala Thr Gly Phe Leu Glu Tyr Phe Asp Met Asn Thr
740 745 750
Asp Pro Tyr Gln Leu Thr Asn Thr Val His Thr Val Glu Arg Gly Ile
755 760 765
Leu Asn Gln Leu His Val Gln Leu Met Glu Leu Arg Ser Cys Gln Gly
770 775 780
Tyr Lys Gln Cys Asn Pro Arg Pro Lys Asn Leu Asp Val Gly Asn Lys
785 790 795 800
Asp Gly Gly Ser Tyr Asp Leu His Arg Gly Gln Leu Trp Asp Gly Trp
805 810 815
Glu Gly

<210> 367

<211> 361
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(361)
<223> n = A,T,C or G

<400> 367
ttnggnttta anaagtacca atttaataat gaatacttan aaatatggna cncagatacc 60
atagtaatat aaaatgcata caatttaaa ttattttctt ataaactctn tacatgaatg 120
gctggcggct tccaacanat aaacttttgg acaaaggnac aanatatttt tgggcattca 180
ttttaaatac catctagtta tccaattagg aggnttctaa aaaaataaat atgacaaata 240
tatggatttc tgaagtataa actgacatac aaatctatat attttcttaa tacttttcat 300
taaagcatct ttaaagcatt ctgtaacatg aagttganag ttcaaattan atgtaatgaa 360
a 361

<210> 368
<211> 558
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(558)
<223> n = A,T,C or G

<400> 368
ccagtgtggt ggaattcgac tcgtctcagg ccagttgcag ccttctcagc caaacgccga 60
ccaaggaaaa ctcactacca tgagaattgc agtgatttgc ttttgcctcc taggcatcac 120
ctgtgccata ccagttaaac aggctgattc tggaagttct gaggaaaagc agctttacaa 180
caantaccca gatgctgtgg ccacatggct aaaccctgac ccatctcaga agcagaatct 240
cctagcccca cagaatgctg tgtcctctga agaaaccaat gactttaaac aagagaccct 300
tccaagtaag tccaacgaaa gccatgacca catggatgat atggatgatg aagatgatga 360
tgaccatgtg gacagccagg actccattga ctcgaacgac tctgatgatg tagatgacac 420
tgatgattct caccagtctg atgagtctca ccattctgat gaatctgatg aactggtcac 480
tgattttccc acggacctgc cagcaaccga agttttcact ccagttgtcc ccacagtaga 540
cacatatgat ggccgagg 558

<210> 369
<211> 1021
<212> DNA
<213> Homo sapiens

<400> 369
tttttacaac atatatcttt aattaaattt atattggkgg gtttaaaaaa cattaagtca 60
ggagatgata gctagggaaa taaggtatcc tgtgagtatt tataacaaaa tatttaaaat 120
ttaaaaagaa taagaaacat caattggctt tttgtaactt aaaagagact aaccaagtgt 180
tgtttcccag ttctgtacaa gcagaggcca caggaggatt cttacataag aagcacaggg 240
aaaagaattg ttaattctgc gtgtgtgttt ttgtttctca gaattgtttg gaagaacttt 300
gtccagtcag aaatgagtaa aaacaagatg taagaaacat taaaacaggg ggcatatggt 360
cttaagagat aatcttggag aatatagcaa aagacaaatt gctccattag atattataat 420
ttggtatgta acatgaacat ttaaaattct gattaaagtg actaaaaggg tttgtttttt 480
aaaaaaaatc aaaacagaac ttacgggata aaactcaaaa taaatttact ctcagtagta 540
acttgatgta ggaatataag tcctctcact ttgataaaca tgaatataaa atattgctgt 600
ctgtattcta gggtttccta cattttctgt aaagagtgat tcatgctatg tcatatgtaa 660
atgactcaac attttgagct aaaaggctgt tcacaatata cacattcttt acttacaaag 720
caaaataagc ttaacacctt tatattaaaa acccgggata cagcaggatt agtagcaccg 780

tgaaaaataa ttcttcccac aaactgcagt cttttatttt actcaatgtg actcttctct 840
taattgaatt tttaatgtac cattttagta actgggcaaa atatataatt ttcatcttat 900
aattcttgga gaaagtcatt ctggacccaa aaagtaaatt cacttcctta tttctttagt 960
agaaaaataa tagagacttt gctctggcgc attgctgagg tacatctgaa tcttcatggt 1020
t 1021

<210> 370
<211> 204
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(204)
<223> n = A,T,C or G

<400> 370
ggaaagcgga agancaggtc ttgatgtgtc ctagaatttt gccatttctg agattgagcc 60
attgaaggca ttccatttct aaagcttatt tagccggtgc ttctaaagaa ttccacacta 120
acgtgataac atggtttttg taacaataaa tgtaggatat ttcctggcac atgcaaataa 180
acctaatcat tgtttcttta aaaa 204

<210> 371
<211> 628
<212> DNA
<213> Homo sapiens

<400> 371
gtgatttcta atcctccctt ttttgattta gttggatgtg cttttaaatg tcctttgcct 60
gcttgaggtg gaaaggggac ctttttgagt tgtcattttg cactttcaaa acttattttc 120
ttggaaaaca atatttatag ggcttaaagc ccattttcat ttctaatcta aattatgtgt 180
gcctatctga aaactttggg ctctttcttg tttctttccc aaaattcaga agttaatggg 240
cttttatgtt tttctatatt ttttttattt caatgatttg gcctgtctat gttaggctaa 300
aaaataacct tgtgtatgct accaacttaa agtgcattat tttgtgtcac ttttttttt 360
cttgtaaaaa tgacttggat tgaaaatatg tggtagcctt tttatttcta cattaagttc 420
tacctaggat atttccaagg actgccacaa aacccatatg tgcagtactt tactactttg 480
ggaaagctgc atctttctac cacattttaa catctaatat atttaatttc tttgaagagg 540
gttctgtgta cgttattgta gttcccagtt taatatagtt ctttgtatct cttaacaggg 600
tggaagttat tgcaaaacac tctggaaa 628

<210> 372
<211> 473
<212> DNA
<213> Homo sapiens

<400> 372
ccagtgtggt ggaattcctg ccgccctgcc gccctgccgc cctgccgccg gtggtcgctg 60
cccgtggtgc tccgtcgccc ccgccacctc acgtcctccc gtgcgtcggg agcgtctcgg 120
ctacaacatg ttgggcatga tcaagaactc gctgttcgga agcgtagaga cgtggccttg 180
gcaggtccta agcaaagggg acaaggaaga agttgcctat gaagaaaggg cctgtgaagg 240
cggcaaattt gccacagtag aagtgacaga taagcctgtg gatgaggctc tacgggaagc 300
aatgcccaag gtcgcaaagt atgcaggggg caccaatgac aagggaattg ggatggggat 360
gacagtccct atttcctttg ctgtgttccc caatgaagat ggctctctgc agaagaaatt 420
aaaagtctgg ttccggattc caaaccaatt tcaaagcgac ccaccagctc cca 473

<210> 373
<211> 283
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(283)
<223> n = A,T,C or G

<400> 373
tttaagtcaa tgccttttat ttttagtttt tctgaagaca aagctcttat aagaatcaca 60
gatgaaagat caggcacaaa tcacattttc ccccttaata acaaaataca aatccaataa 120
ttttagaaaa tcagttttta gtgacccana tgcctggaga aaagctgcca ggatttttct 180
ggtctatcgc agaattttct acatcaatga gaaggatgct gcatatcttg gctgtattat 240
ttcctaccgn gagaaaagaa acttaatata tggaacatgc ttt 283

<210> 374
<211> 529
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(529)
<223> n = A,T,C or G

<400> 374
tccagngtgg tggaattccg cgcgcggggc gctgctgctg gcgctgctgc tggctcgggc 60
tggactcagg aagccggagt cgcaggaggc ggcgccctta tcaggaccat gcggccgacg 120
ggtcatcacg tcgcgcatcg tgggtggaga ggacgccgaa ctcgggcgtt ggccgtggca 180
ggggagcctg cgcctgtggg attcccacgt atgcggagtg agcctgctca gccaccgctg 240
ggcactcacg gcggcgcact gctttgaaac tgaccttagt gatccctccg ggtggatggt 300
ccagtttggc cagctgactt ccatgccatc cttctggagc ctgcaggcct actacacccg 360
ttacttcgta tcgaatatct atctgagccc tcgctacctg gggaattcac cctatgacat 420
tgccttggtg aagctgtctg cacctgtcac ctacactaaa cacatccagc ccatctgtct 480
ccaggccttc acatttgagt ttgagaaccg gacagactgc tgggtgact 529

<210> 375
<211> 519
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(519)
<223> n = A,T,C or G

<400> 375
tttgaattta naccaagaac ttctcaataa aagaaaatca tgaatgctcc acaatttcaa 60
cataccacaa gagaagttaa tttcttaaca ttgtgttcta tgattatttg taagaccttc 120
accaagttct gatatctttt aaagacatag ttcaaaattg cttttgaaaa tctgtattct 180
tgaaaatatc cttgttgtgt attaggtttt taaataccag ctaaaggatt acctcactga 240
gtcatcagta ccctcctatt cagctcccca agatgatgtg tttttgctta ccctaagaga 300
ggttttcttc ttatttttag ataattcaag tgcttagata aattatgttt tctttaagtg 360
tttatggtaa actcttttaa agaaaattta atatgttata gctgaatctt tttggtaact 420
ttaaatcttt atcatagact ctgtacatat gttcaaatta gctgcttgcc tgatgtgtgt 480
atcatcggtg ggatgacaga acaaacatat ttatgatca 519

<210> 376
<211> 171
<212> DNA
<213> Homo sapiens

<400> 376
tcaagattta gccaaggctg tggcaaaggt gtaacttgta aacttgagtt ggagtactat 60
atttacaaat aaaattggca ccatgtgcca tctgtacata ttactgttgc atttactttt 120
aataaagctt gtggcccctt ttacttttt atagcttaaa aaaaaaaaa a 171

<210> 377
<211> 270
<212> DNA
<213> Homo sapiens

<400> 377
ccagtgtggt ggaattaatc aggcctccca aatttagcag gtgctgggga ggaccctagg 60
gagtggttta tgggggctag ctggtgaaac tgcccttcc tttctgttct atgagtgtga 120
tggtgtttga gaaaatgtgg ggctatggtt caggcgcact tcacatgtgc aaagatggag 180
aaagcactca cctacacgtt taggctcaga atattgattg aaacattttg aatgatcaaa 240
aataaaatgt tatttttaaa gtttcaaaaa 270

<210> 378
<211> 416
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(416)
<223> n = A,T,C or G

<400> 378
ccagtgtggt ggaattcgcc actgctaggg tttacaggtc atccctggat taaataagtg 60
atattgtgtt tttttttctt ttgacacaaa gtaaaattat aattaatatt gaataaagta 120
aaaatgaact ccagtgnggn ggaattcggc actcaggaaa tattagttgc atgaacgaag 180
gctgcatttt catcanaaca acatgcagtt caaccccttc atgtttcaat gagggttcan 240
atncccanag ggctatgcta tcatcctgga gcccactctg ctaacaatta gcanaacgga 300
agccttaatt tccanattct agtgaacttg atgagtcaan actattgcaa ttggaaatct 360
gttctcctct gctgctgcat tccctgctta atactcaagc canaaaccag gaaggt 416

<210> 379
<211> 576
<212> DNA
<213> Homo sapiens

<400> 379
ttcctatgat cattaaactc attctcaggg ttaagaaagg aatgtaaatt tctgcctcaa 60
tttgtacttc atcaataagt ttttgaagag tgcagatttt tagtcaggtc ttaaaaataa 120
actcacaaat ctggatgcat ttctaaattc tgcaaatgtt tcctggggtg acttaacaag 180
gaataatccc acaatatacc tagctaccta atacatggag ctggggctca acccactgtt 240
tttaaggatt tgcgcttact tgtggctgag gaaaaataag tagttcgagg aagtagtttt 300
taaatgtgag cttatagata gaaacagaat atcaacttaa ttatgaaatt gttagaacct 360
gttctcttgt atctgaatct gattgcaatt actattgtac tgatagactc cagccattgc 420
aagtctcaga tatcttagct gtgtagtgat tcttgaaatt ctttttaaga aaaattgagt 480
agaaagaaat aaacccttg taaatgaggc ttggcttttg tgaaagatca tccgcaggct 540
atgttaaaag gattttagct cactaaaagt gtaata 576

<210> 380
<211> 347
<212> DNA
<213> Homo sapiens

<400> 380
ccagtgtggt ggaattcgga gagaaggaag cctggggccc agccgaggaa gcgaaaaacc 60
aaacaagcag ttcccattgt ggaaccccaa gaacctgaga tcaaactaaa atatgccacc 120
cagccactgg ataaaactga tgccaagaac aagtcttttt acccttacat ccatgtagta 180
aataagtgtg aacttggagc cgtttgtaca atcatcaatg ctgaggaaga agaacagacc 240
aaattagtga ggggcaggaa gggtcagagg tcactgaccc ctccacctag cagcactgaa 300
agcaaggcgc tcccggcctc gtcctttatg ctgcagggac ctgttgt 347

<210> 381
<211> 258
<212> DNA
<213> Homo sapiens

<400> 381
gacaagctcc tggtcttgag atgtcttctc gttaaggaga tgggcctttt ggaggtaaag 60
gataaaatga atgagttctg tcatgattca ctattctaga acttgcatga cctttactgt 120
gttagctctt tgaatgttct tgaaatttta gactttcttt gtaaacaaat gatatgtcct 180
tatcattgta taaaagctgt tatgtgcaac agtgtggaga ttccttgtct gatttaataa 240
aatacttaaa cactgaaa 258

<210> 382
<211> 580
<212> DNA
<213> Homo sapiens

<400> 382
gccgtaggga gtacctgctg ccccagctga ctgtggcccc ctccgtgatc catccatctc 60
cagggagcaa gacagagacg caggaatgga aagcggagtt cctaacagga tgaaagttcc 120
cccatcagtt cccccagtac ctccaagcaa gtagctttcc acatttgtca cagaaatcag 180
aggagagatg gtgttgggag ccctttggag aacgccagtc tcccaggccc cctgcatcta 240
tcgagtttgc aatgtcacaa cctctctgat cttgtgctca gcatgattct ttaatagaag 300
ttttattttt tcgtgcactc tgctaatcat gtgggtgagc cagtggaaca gcgggagacc 360
tgtgctagtt ttacagattg cctcctaatg acgcggctca aaaggaaacc aagtggtcag 420
gagttgtttc tgacccactg atctctacta ccacaaggaa aatagtttag gagaaaccag 480
cttttactgt ttttgaaaaa ttacagcttc accctgtcaa gttaacaagg aatgcctgtg 540
ccaataaaag gtttctccaa cttgaagtct actctgaaaa 580

<210> 383
<211> 608
<212> DNA
<213> Homo sapiens

<400> 383
gtgctagatg aaaagcgtgc aatatgyttt aaagctatca acaaaaactg aatattataa 60
gcaagcaata tcatagtaat tggcagatta gctcatattc tatacagcat cgtttaaata 120
ggaaaaattt aatgctagca aaaaataaat ttagaaatat ggcatgacat gaaaatacaa 180
tcttatattt acaccagctt ttcactaata ttttgtacct aaggtgatgg ggaactccat 240
tcagataata aaattctctt tcagctagag aagttaacag gaataaatat atgaacaaaa 300
aagctgcaag gataaatgtg gagaaaatga tgagaattag ctaacatttt taagtttttt 360
taaactttct tcccctcact tagttgtact taatatttag tggaaagtaa taatttttt 420
aattttctat caactaatag tatagtaact atgattaact tgtttacttt ttctgaggat 480
tagtaaatca attttttttt tatttcaaat ttttggattt acacttgagg gtaaattaaa 540
tctggtaaac tgaatttcct agttaaataa aattagttgc agtatatgat gaacagtgta 600
tgactcaa 608

<210> 384
<211> 585
<212> DNA
<213> Homo sapiens

<400> 384
ttatttcctt aaatattgct acaaaaggaa gatgcgggtg taagccctga ttttttttc 60
tcccaagaaa aatcttaaag gaccacttta gataatattt gattcctact gtaaaattta 120
gaaaatgatg aattcttgtc cattttgta atcaagattt taggaaaaac agaagtacat 180
ctatctttat gaaattttgg gcaggttttt gtgtatcaat attttgtact tttagggaat 240
attttatttt ttagttattt gtgtcaaatt ataattataa aaggtacagc agaaaatata 300
ccatgttttt atataggttc acacctgtac ttaggaggga ccctgtccat ctatatactt 360
tttgtataaa attttaaaat gttaaagatc cacaaggtct taataaaatg attctatagc 420
tagaaaaaca tttaccttcc cagtgctttg cactaaaata tactgtgaaa ggaaactaga 480
aagactgtaa ctattgctgg aaatgttcta tattgaatgt acatgctctt gttggaaaaa 540
tgtctatatg tgatggaaat aaaccagaat cgaagttatt tcaaa 585

<210> 385
<211> 511
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(511)
<223> n = A,T,C or G

<400> 385
atattgtaca gtatttatcg agataaacat ggtwatcaaa atgtccattg tttataagct 60
gagaatttgc caatattttt caaggagagg cttcttgctg aattttgatt ctgcagctga 120
aatttaggac agttgcaaac gtgaaaagaa gaaaattatt caaatttgga cattttaatt 180
gtttaaaaat tgtacaaaag gaaaaaatta gaataagtac tggcgaacca tctctgtggt 240
cttgtttaaa aagggcaaaa gttttagact actaaatttt ttaacagtaa gttataaaat 300
ttagtagtct aaaacttata acttactgtt aaaagcaaaa atggccatgc aggttgacac 360
cgttggtaat ttataatagc ttttgttcga tcccaacttt ccattttgtt cagataaaaa 420
aaaccatgaa attactgngt ttgaaatatt ttcttatggt ttgtaatatt tctgtaaatt 480
tattgtgata ttttaaggnt ttccccccct t 511

<210> 386
<211> 311
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(311)
<223> n = A,T,C or G

<400> 386
gtggaattcc atgaatntag ttcccatcat gacttanaag gtgctgtagg tgggtactac 60
ccagaaccca gtnagctttg tcacttggat caaagtgatt ctgatttcca tggagatctt 120
acatttcaac acgtatttca taaccacact taccacttac agccaactgc accagaatct 180
acttctgaac cttttccgtg gcctgggaag tcacagaaga taaggagtag ataccttgaa 240
gacacagata gaaacttgag ccgtgatgaa cagcgngcta aagctttgca tatccctttt 300
tctgtagatg a 311

<210> 387
<211> 461
<212> DNA
<213> Homo sapiens

<400> 387
cacagatagc aagacttcat ttcaggagtt gggagtggga agtaggaagt gtttaatccc 60

aagttttggt gccctaaaat ggctagtagt atagttaatt ctcaattctc tagctgtgat 120
cttctgtgcc ttctatctct tcctaaggaa aaccacatta gatgaaccca gggctcagtc 180
attttaggga gagggttgag acaacactgc cagcaacaca gctggaatca cccgagtcgg 240
gaacattaaa gttcctgaga gaatatgaaa caactatcaa cataatattt ctccctactt 300
ttacagtaaa atattggaag taaataaata tagggaatgc aacaactggc taggagtgtt 360
ttacattcag ttgtttggaa gcataacaca ttcagctcct ttgaatcttc ccgttagaaa 420
atacagaatt actctatcac cttttaaggt acagtaaaaa a 461

<210> 388
<211> 555
<212> DNA
<213> Homo sapiens

<400> 388
ggataaaggc cagggatgct gctcaacctc ctaccatgta caggacgtct ccccattaca 60
actacccaat ccgaagtgtc aactgtgtca ggactaagaa accctggttt tgagtagaaa 120
agggcctgga aagaggggag ccaacaaatc tgtctgcttc ctcacattag tcattggcaa 180
ataagcattc tgtctctttg gctgctgcct cagcacagag agccagaact ctatcgggca 240
ccaggataac atctctcagt gaacagagtt gacaaggcct atgggaaatg cctgatggga 300
ttatcttcag cttgttgagc ttctaagttt ctttcccttc attctaccct gcaagccaag 360
ttctgtaaga gaaatgcctg agttctagct caggttttct tactctgaat ttagatctcc 420
agacccttcc tggccacaat tcaaattaag gcaacaaaca tataccttcc atgaagcaca 480
cacagacttt tgaaagcaag gacaatgact gcttgaattg aggccttgag gaatgaagct 540
ttgaaggaaa agaat 555

<210> 389
<211> 563
<212> DNA
<213> Homo sapiens

<400> 389
ttattttggt cagctgagta ccatcaggat atttaaccct ttaagtgctg ttttgggagt 60
agaaaactaa agcaacaata cttcctcttg acagctttga ttggaatggg gttattagat 120
cattcacctt ggtcctacac tttttaggat gcttggtgaa cataacacca cttataatga 180
acatccctgg ttcctatatt ttgggctatg tgggtaggaa ttgttacttg ttactgcagc 240
agcagcccta gaaagtaagc ccagggcttc agatctaagt tagtccaaaa gctaaatgat 300
ttaaagtcaa gttgtaatgc taggcataag cactctataa tacattaaat tataggccga 360
gcaattaggg aatgtttctg aaacattaaa cttgtattta tgtcactaaa attctaacac 420
aaacttaaaa aatgtgtctc atacatatgc tgtactaggc ttcatcatgc atttctaaat 480
ttgtgtatga tttgaatata tgaaagratt tatacaagag tgttatttaa aattattaaa 540
aataaatgta tataatttga aaa 563

<210> 390
<211> 278
<212> DNA
<213> Homo sapiens

<400> 390
gaacattatg ttttagatgg gtagtactag ctactcatct gtcccccaga aacccaagct 60
aagcatggac atattgaaga gaatgtcagc accattaaaa aaactctaga aaaatcacat 120
gtgatgactg aggttaattc agtctgtcaa ttacatcagt ataattgcct tcttgtaacc 180
ctaagtatgg tgaagcagaa ttgaattcta caaaagtctt tcatctgttt tcctatggaa 240
taattaacaa acccaataaa tgtataaata gcatgaaa 278

<210> 391
<211> 578
<212> DNA
<213> Homo sapiens

<400> 391
cggcgctcgg ctcgcaggat ggatcccgta cccgggacag actcggcgcc gctggctggc 60
ctggcctggt cgtcggcctc tgcacccccg ccgcgggggt tcagcgcgat ctcctgcacc 120
gtcgaggggg cacccgccag ctttggcaag agcttcgcgc agaaatctgg ctacttcctg 180
tgccttagtt ctctgggcag cctagagaac ccgcaggaga acgtggtggc cgatatccag 240
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<210> 392
<211> 439
<212> DNA
<213> Homo sapiens

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aattctgtat gtatatattc actttctgac atttagatat gccaaaagaa ttaaaatcaa 420
aagcactaag aaataaaaa 439

<210> 393
<211> 544
<212> DNA
<213> Homo sapiens

<400> 393
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agat 544

<210> 394
<211> 424
<212> DNA
<213> Homo sapiens

<400> 394
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aaaa 424

<210> 395
<211> 279
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(279)
<223> n = A,T,C or G

<400> 395
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<210> 396
<211> 3293
<212> DNA
<213> Homo sapiens

<400> 396
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<210> 397
<211> 727
<212> PRT
<213> Homo sapiens

<400> 397
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Glu Val Ser Arg Glu Thr Gln Arg Thr Pro Met Asn His Gln Lys Ala
35 40 45
Val Asn Asp Glu Thr Cys Lys Ala Ser His Ile Thr Ser Ser Val Phe
50 55 60
Pro Ser Ala Ser Leu Gly Lys Ala Ser Ser Arg Lys Pro Phe Gly Ile
65 70 75 80
Leu Ser Pro Asn Val Leu Cys Ser Met Ser Gly Lys Ser Pro Val Glu
85 90 95
Ser Ser Leu Asn Val Lys Thr Lys Lys Asn Ala Pro Ser Ala Thr Ile
100 105 110
His Gln Gly Glu Glu Glu Gly Pro Leu Asp Ile Trp Ala Val Val Lys
115 120 125
Pro Gly Asn Thr Lys Glu Lys Ile Ala Phe Phe Ala Ser His Gln Cys
130 135 140
Ser Asn Arg Ile Gly Ser Met Lys Ile Lys Ser Ser Trp Asp Ile Asp
145 150 155 160
Gly Arg Ala Thr Lys Arg Arg Lys Lys Ser Gly Asp Leu Lys Lys Ala
165 170 175
Lys Val Gln Val Glu Arg Met Arg Glu Val Asn Ser Arg Cys Tyr Gln
180 185 190
Pro Glu Pro Phe Ala Cys Gly Ile Glu His Cys Ser Val His Tyr Val
195 200 205
Ser Asp Ser Gly Asp Gly Val Tyr Ala Gly Arg Pro Leu Ser Val Ile
210 215 220
Gln Met Val Ala Phe Leu Glu Gln Arg Ala Ser Ala Leu Leu Ala Ser
225 230 235 240
Cys Ser Lys Asn Cys Thr Asn Ser Pro Ala Ile Val Arg Phe Ser Gly
245 250 255

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Gln Ser Arg Gly Val Pro Ala Val Ser Glu Ser Tyr Ser Ala Pro Gly
            260                 265                 270
Ala Cys Glu Glu Pro Thr Glu Arg Gly Asn Leu Glu Val Gly Glu Pro
        275                 280                 285
Gln Ser Glu Pro Val Arg Val Leu Asp Met Val Ala Lys Leu Glu Ser
    290                 295                 300
Glu Cys Leu Lys Arg Gln Gly Gln Arg Glu Pro Gly Ser Leu Ser Arg
305                 310                 315                 320
Asn Asn Ser Phe Arg Arg Asn Val Gly Arg Val Leu Leu Ala Asn Ser
                325                 330                 335
Thr Gln Ala Asp Glu Gly Lys Thr Lys Lys Gly Val Leu Glu Ala Pro
            340                 345                 350
Asp Thr Gln Val Asn Pro Val Gly Ser Val Ser Val Asp Cys Gly Pro
        355                 360                 365
Ser Arg Ala Asp Arg Cys Ser Pro Lys Glu Asp Gln Ala Trp Asp Gly
    370                 375                 380
Ala Ser Gln Asp Cys Pro Pro Leu Pro Ala Gly Val Ser Phe His Ile
385                 390                 395                 400
Asp Ser Ala Glu Leu Glu Pro Gly Ser Gln Thr Ala Val Lys Asn Ser
                405                 410                 415
Asn Arg Tyr Asp Val Glu Met Thr Asp Glu Leu Val Gly Leu Pro Phe
            420                 425                 430
Ser Ser His Thr Tyr Ser Gln Ala Ser Glu Leu Pro Thr Asp Ala Val
        435                 440                 445
Asp Cys Met Ser Arg Glu Leu Val Ser Leu Thr Ser Arg Asn Pro Asp
    450                 455                 460
Gln Arg Lys Glu Ser Leu Cys Ile Ser Ile Thr Val Ser Lys Val Asp
465                 470                 475                 480
Lys Asp Gln Pro Ser Ile Leu Asn Ser Cys Glu Asp Pro Val Pro Gly
                485                 490                 495
Met Leu Phe Phe Leu Pro Pro Gly Gln His Leu Ser Asp Tyr Ser Gln
            500                 505                 510
Leu Asn Glu Ser Thr Thr Lys Glu Ser Ser Glu Ala Ser Gln Leu Glu
        515                 520                 525
Asp Ala Ala Gly Gly Asp Ser Ala Ser Glu Glu Lys Ser Gly Ser Ala
    530                 535                 540
Glu Pro Phe Val Leu Pro Ala Ser Ser Val Glu Ser Thr Leu Pro Val
545                 550                 555                 560
Leu Glu Ala Ser Ser Trp Lys Lys Gln Val Ser His Asp Phe Leu Glu
                565                 570                 575
Thr Arg Phe Lys Ile Gln Gln Leu Leu Glu Pro Gln Gln Tyr Met Ala
            580                 585                 590
Phe Leu Pro His His Ile Met Val Lys Ile Phe Arg Leu Leu Pro Thr
        595                 600                 605
Lys Ser Leu Val Ala Leu Lys Cys Thr Cys Cys Tyr Phe Lys Phe Ile
    610                 615                 620
Ile Glu Tyr Tyr Asn Ile Arg Pro Ala Asp Ser Arg Trp Val Arg Asp
625                 630                 635                 640
Pro Arg Tyr Arg Glu Asp Pro Cys Lys Gln Cys Lys Lys Lys Tyr Val
                645                 650                 655
Lys Gly Asp Val Ser Leu Cys Arg Trp His Pro Lys Pro Tyr Cys Gln
            660                 665                 670
Ala Leu Pro Tyr Gly Pro Gly Tyr Trp Met Cys Cys His Arg Ser Gln
        675                 680                 685
Lys Gly Phe Pro Gly Cys Lys Leu Gly Leu His Asp Asn His Trp Val
    690                 695                 700
Pro Ala Cys His Ser Phe Asn Arg Ala Ile His Lys Lys Ala Lys Gly
705                 710                 715                 720
Thr Glu Ala Glu Glu Glu Tyr
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725

<210> 398
<211> 403
<212> DNA
<213> Homo sapiens

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cactatgtcg ggtggcctcc tgaaggcgct gcgcagcgac tcctacgtgg agctgagcca 120
gtaccgggac cagcacttcc ggggtgacaa tgaagaacaa gaaaaattac tgaagaaaag 180
ctgtacgtta tatgttggaa atctttcttt ttacacaact gaagaacaaa tctatgaact 240
cttcagcaaa agtggtgaca taaagaaaat cattatgggt ctggataaaa tgaagaaaac 300
agcatgtgga ttctgttttg tggaatatta ctcacgcgca gatgcggaaa acgccatgcg 360
gtacataaat gggacgcgtc tggatgaccg aatcattcgc aca 403

<210> 399
<211> 403
<212> DNA
<213> Homo sapiens

<400> 399
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accaccaagg agtgtggaat gtccttgagt gtattattta tgcaagtcac agtcacgttg 120
ccatcatggc agctatgtga aacactaata aatgtgtttt tacttttttat tcccgttaaa 180
actgatgtaa aacaggataa aggcttgtta tagtcactta taagtatctg ggtctaagta 240
atttccttag atgtttctaa agaaacattt tcagctttgc tcccattatg attccaataa 300
ggaacgcttt cctagtgcaa ttttaggagt aaagtttgaa gagataaaaa tagccaaaga 360
taggagacgt ctgaattttg aatgataaac agtgatgttt taa 403

<210> 400
<211> 283
<212> DNA
<213> Homo sapiens

<400> 400
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tcttgactga tggtgttccc tttaaccctt ggcatgtata atagaatttt ggtgaatgaa 180
agaacccaaa taggccagat agtcccccca ggccctgata tccataaaag gcttgggaat 240
gcattatgta attgtcctta gtctttttgt tgttttagaa aaa 283

<210> 401
<211> 303
<212> DNA
<213> Homo sapiens

<400> 401
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cctggacctc aaggtcatcc acttggtgcg tgatccccgc gcggtggcga gttcacggat 120
ccgctcgcgc cacggcctca tccgtgagag cctacaggtg gtgcgcagcc gagacccgcg 180
agctcaccgc atgcccttct tggaggccgc gggccacaag cttggcgcca agaaggaggg 240
cgtgggcggc cccgcagact accacgctct gggcgctatg gaggtcatct gcaatagtat 300
ggc 303

<210> 402
<211> 473
<212> DNA

<213> Homo sapiens

<400> 402
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accaggatcc atttaggtac cacttgatat aaaaaggata tccataatga atattttata 120
ctgcatcctt tacattagcc actaaatacg ttattgcttg atgaagacct ttcacagaat 180
cctatggatt gcagcatttc acttggctac ttcataccca tgccttaaag aggggcagtt 240
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aagggcagct ggcccccaat gtggggaggt ccgaacattt tctgaattcc cattttcttg 360
ttcgcggcta aatgacagtt tctgtcatta cttagattcc gatctttccc aaaggtgttg 420
atttacaaag aggccagcta atagcagaaa tcatgaccct gaaagagaga tga 473

<210> 403
<211> 513
<212> DNA
<213> Homo sapiens

<400> 403
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taaaagtgtg gccactgagc atttgatttt ataggaaaaa atagtatttt tgagaataac 360
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tggaaaaata gaagtgtaaa atgttaataa tac 513

<210> 404
<211> 533
<212> DNA
<213> Homo sapiens

<400> 404
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<210> 405
<211> 513
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(513)
<223> n = A,T,C or G

<400> 405
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tcgaaggcca tcaagaattt actgaaagca gttagcaagg aaaggtctaa aagatctcct 360
taaaaccaga ggggagcaaa atcgatgcag tgcttccaag gatggaccac acagaggctg 420
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gttacactaa aaggtgacca atcatggtca cca 513

<210> 406
<211> 483
<212> DNA
<213> Homo sapiens

<400> 406
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ctggagatag gcagggctaa aaaggtatta ttatttttcc tttaatgatg gtgctaaaat 420
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act 483

<210> 407
<211> 241
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(241)
<223> n = A,T,C or G

<400> 407
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agactnggct ttgtttttg tgctattagg aaattctgat gagcattact attcactgat 180
gcagaaagac gttcttttgc ataaaagact ttttttaaca ctttggactt ctctgaaata 240
t 241

<210> 408
<211> 213
<212> DNA
<213> Homo sapiens

<400> 408
ccagtgtggt ggaattcaca tgatacagcc actgggctta tacagtatgc attggaccag 60
ggcgtgaacg tcacccaggt attcgtggac accgtaggga tgccagagac ataccaggcg 120
cggttgcagc aaagttttcc cgggattgag gggaccggcc aaggccaaag cagatgccct 180
ctacccggtg gttagtgctg ccagcatctg tgc 213

<210> 409
<211> 413
<212> DNA
<213> Homo sapiens

<400> 409
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tatttgaact cttaagtcat aaatgtataa tgacttatga attagcacag ttaagttgac 120
actagaaact gcccatttct gtattacact atcaaatagg aaacattgga aagatgggga 180

aaaaaatctt attttaaaat ggcttagaaa gttttcagat tactttgaaa attctaaact 240
tctttctgtt tccaaaactt gaaaatatgt agatggactc atgcattaag actgttttca 300
aagctttcct cacatttta aagtgtgatt ttccttttaa tatacatatt tattttcttt 360
aaagcagcta tatcccaacc catgactttg gagatatacc tataaaacca ata 413

<210> 410
<211> 153
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(153)
<223> n = A,T,C or G

<400> 410
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taganaatat gaagaatgca tgtcaaaaga tct 153

<210> 411
<211> 253
<212> DNA
<213> Homo sapiens

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<213> Homo sapiens

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35 40 45
His Glu Leu Gly Lys Tyr Lys Asp Leu Leu Met Lys Ala Glu Thr Glu
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Arg Ser Ala Leu Asp Val Lys Leu Lys His Ala Arg Asn Gln Val Asp
65 70 75 80
Val Glu Ile Lys Arg Arg Gln Arg Ala Glu Ala Asp Cys Glu Lys Leu
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Glu Arg Gln Ile Gln Leu Ile Arg Glu Met Leu Met Cys Asp Thr Ser
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145 150 155 160
Thr Asp Glu Ser Leu Asp Trp Asp Ser Ser Leu Val Lys Thr Phe Lys

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225                 230                 235                 240
Tyr Trp Thr Arg Ser Arg Arg Lys Thr Gly Thr Leu Gln Pro Trp Asn
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Ser Asp Ser Thr Leu Asn Ser Arg Gln Leu Glu Pro Arg Thr Glu Thr
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Asp Ser Val Gly Thr Pro Gln Ser Asn Gly Gly Met Arg Leu His Asp
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Phe Val Ser Lys Thr Val Ile Lys Pro Glu Ser Cys Val Pro Cys Gly
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Lys Arg Ile Lys Phe Gly Lys Leu Ser Leu Lys Cys Arg Asp Cys Arg
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Val Val Ser His Pro Glu Cys Arg Asp Arg Cys Pro Leu Pro Cys Ile
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Pro Thr Leu Ile Gly Thr Pro Val Lys Ile Gly Glu Gly Met Leu Ala
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Asp Phe Val Ser Gln Thr Ser Pro Met Ile Pro Ser Ile Val Val His
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Cys Val Asn Glu Ile Glu Gln Arg Gly Leu Thr Glu Thr Gly Leu Tyr
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        515                 520                 525
Glu Arg Leu Leu Ser Leu Pro Leu Glu Tyr Trp Ser Gln Phe Met Met
    530                 535                 540
Val Glu Gln Glu Asn Ile Asp Pro Leu His Val Ile Glu Asn Ser Asn
545                 550                 555                 560
Ala Phe Ser Thr Pro Gln Thr Pro Asp Ile Lys Val Ser Leu Leu Gly
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Pro Val Thr Thr Pro Glu His Gln Leu Leu Lys Thr Pro Ser Ser Ser
            580                 585                 590
Ser Leu Ser Gln Arg Val Arg Ser Thr Leu Thr Lys Asn Thr Pro Arg
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<211> 3061
<212> DNA
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<213> Homo sapiens

<400> 424
gaattcggca cgagcagccc tcggctgagc cgcgccgcac catgcccgcc gtggacaagc 60
tcctgctaga ggaggcgttg caggacagcc cccagactcg ctctttactg agcgtgtttg 120
aagaagatgc tggcaccctc acagactata ccaaccagct gctccaggca atgcagcgcg 180
tctatggagc ccagaatgag atgtgcctgg ccacacaaca gctttctaag caactgctgg 240
catatgaaaa acagaacttt gctcttggca aaggtgatga agaagtaatt tcaacactcc 300
actatttttc caaagtggtg gatgagctta atcttctcca tacagagctg gctaaacagt 360
tggcagacac aatggttcta cctatcatac aattccgaga aaaggatctc acagaagtaa 420
gcactttaaa ggatctattt ggactcgcta gcaatgagca tgacctctca atggcaaaat 480
acagcaggct gcctaagaaa aaggagaatg agaaggtgaa gaccgaagtc ggaaaagagg 540
tggccgcggc ccggcggaag cagcacctct cctcccttca gtactactgt gccctcaacg 600
cgctgcagta cagaaagcaa atggccatga tggagcccat gataggcttt gcccatggac 660
agattaactt ttttaagaag ggagcagaga tgttttccaa acgtatggac agctttttat 720
cctccgttgc agacatggtt caaagcattc aggtagaact ggaagccgag gcggaaaaga 780
tgcgggtgtc ccagcaagaa ttactttctg ttgatgaatc tgtttacact ccagactctg 840
atgtggccgc accacagatc aacaggaacc tcatccagaa ggctggttac cttaatctta 900
gaaacaaaac agggctggtc accaccacct gggagaggct ttatttcttc acccaaggcg 960
ggaatctcat gtgtcagccc aggggagccg tggctggagg tttgatccag gacctggaca 1020
actgctcagt gatggccgtg gattgcgaag accggcgcta ctgcttccag atcaccacgc 1080
ccaatggaaa atcgggaata atcctccagg ctgagagcag aaaggaaaat gaagagtgga 1140
tatgtgcaat aaacaacacc tccagacaga tctacctgac cgacaaccct gaggccgtcg 1200
cgatcaagtt gaatcagacc gctctgcaag cagtgactcc cattacaagt tttggaaaaa 1260
aacaagaaag ctcatgcccc agccagaacc tgaaaaattc agagatggaa aatgaaaatg 1320
acaagattgt tcccaaagca acagccagtc tacctgaagc agaggagctg atcgcgcctg 1380
gaacgccgat tcaattcgat attgtgcttc ctgctacaga attccttgat cagaacagag 1440
ggagcaggcg taccaaccct tttggtgaaa ctgaggatga atcatttcca gaagcagaag 1500
attctctttt gcagcagatg tttatagttc ggtttttggg atcaatggca gttaaaacag 1560
acagcactac ttgaagtgat ttatgaagcg atgagacaag tattggctgc tcgggctatt 1620
cataacatct tccgcatgac agaatcccat ctgatggtca ccagtcaatc tttgaggttg 1680
atagatccac agactcaagt atcaagggcc aattttgaac ttaccagtgt cacacaattt 1740
gctgctcatc aagaaaacaa gagactggtt ggttttgtca tccgtgttcc tgaatccact 1800
ggagaagaat ctctgagtac atacattttt gaaagcaact cagaaggcga aaagatatgt 1860
tatgctatta atttgggaaa agaaattatt gaggttcaga aggatccaga agcactggct 1920
caattaatgc tgtccatacc actaaccaat gatggaaaat atgtactgtt aaacgatcaa 1980

ccagatgacg atgatggaaa tccaaatgaa catagaggcg cagaatccga agcataactc 2040
acttgcgcct gtgggggaag agcaaacagg aaggagagct acctcctaag ggttttaacg 2100
tctctgacat acaggcacac tgacctgatt tccgaaggct gacaatcgtt tgtggaatgt 2160
aatcttgatg ccttgatact gagacttggg agggaaacta agaaatggtt gacagcgttc 2220
ccacccatct acaatgttat tttaggtgct ttgtggtaag tctttttttct tagattgcgc 2280
taaaatttct tagattgttc agcgctcaga acaaaagttt gaaaaatgca ttgttcatat 2340
gaatgtcatc tcttttcagt ttccagtatc ctttttaaaa aatggcaaaa gcctagattt 2400
acaatttgat gaacactaaa tatttcttat taatataatc tatttttgta ttttacttaa 2460
tgagctttaa gtgcctgtcg ttctgaaaat tgtgtattta taattcagct tatctcacaa 2520
ttggacctaa tagcatttct ttgtgcagtt aggtgacgag cactgctttg aggcccaagc 2580
actagtagag atgcgcgata caggtctagt ttcggtaact gttccagaca tcaagcaata 2640
aaaaaatgaa taccacaaaa gatgtttgat tttacagtgg agccttactg aaccagcatt 2700
cagaagttta aggtcctcct aggtatgagt atttttagta gtggatcact gtggacaggg 2760
tgcagctcta ccagttcctg tttcttctga gccagaccct cttcagggaa gggaccaatt 2820
aattttaaaa ctcacttgaa gcacagctgg tcatggggct tggtataaag ttcctatttc 2880
caccctgata cttccaattc ctggaacccc agcccactcc cccatccctc ctccctatca 2940
aactagtata atgattttga atcggtacag tgtgtttaac tgtaactaag ttcaacagac 3000
tattattatc tttgtaataa attaacctag caataaaaat tattctgttt caaaaaaaaa 3060
aaaaaacaac tcgag 3075

<210> 425
<211> 819
<212> PRT
<213> Homo sapiens

<400> 425
Gly Asp Phe Gly Gly Gly Ser Ser Leu Ala Ala Gly Met Ala Gly Thr
1 5 10 15
Val Val Leu Asp Asp Val Glu Leu Arg Glu Ala Gln Arg Asp Tyr Leu
20 25 30
Asp Phe Leu Asp Asp Glu Glu Asp Gln Gly Ile Tyr Gln Ser Lys Val
35 40 45
Arg Glu Leu Ile Ser Asp Asn Gln Tyr Arg Leu Ile Val Asn Val Asn
50 55 60
Asp Leu Arg Arg Lys Asn Glu Lys Arg Ala Asn Arg Leu Leu Asn Asn
65 70 75 80
Ala Phe Glu Glu Leu Val Ala Phe Gln Arg Ala Leu Lys Asp Phe Val
85 90 95
Ala Ser Ile Asp Ala Thr Tyr Ala Lys Gln Tyr Glu Glu Phe Tyr Val
100 105 110
Gly Leu Glu Gly Ser Phe Gly Ser Lys His Val Ser Pro Arg Thr Leu
115 120 125
Thr Ser Cys Phe Leu Ser Cys Val Val Cys Val Glu Gly Ile Val Lys
130 135 140
Cys Ser Leu Val Arg Pro Lys Val Val Arg Ser Val His Tyr Cys Pro
145 150 155 160
Ala Thr Lys Lys Thr Ile Glu Arg Arg Tyr Ser Asp Leu Thr Thr Leu
165 170 175
Val Ala Phe Pro Ser Ser Ser Val Tyr Pro Thr Lys Asp Glu Glu Asn
180 185 190
Asn Pro Leu Glu Thr Glu Tyr Gly Leu Ser Val Tyr Lys Asp His Gln
195 200 205
Thr Ile Thr Ile Gln Glu Met Pro Glu Lys Ala Pro Ala Gly Gln Leu
210 215 220
Pro Arg Ser Val Asp Val Ile Leu Asp Asp Asp Leu Val Asp Lys Ala
225 230 235 240
Lys Pro Gly Asp Arg Val Gln Val Val Gly Thr Tyr Arg Cys Leu Pro
245 250 255
Gly Lys Lys Gly Gly Tyr Thr Ser Gly Thr Phe Arg Thr Val Leu Ile

260 265 270
Ala Cys Asn Val Lys Gln Met Ser Lys Asp Ala Gln Pro Ser Phe Ser
275 280 285
Ala Glu Asp Ile Ala Lys Ile Lys Lys Phe Ser Lys Thr Arg Ser Lys
290 295 300
Asp Ile Phe Asp Gln Leu Ala Lys Ser Leu Ala Pro Ser Ile His Gly
305 310 315 320
His Asp Tyr Val Lys Lys Ala Ile Leu Cys Leu Leu Leu Gly Gly Val
325 330 335
Glu Arg Asp Leu Glu Asn Gly Ser His Ile Arg Gly Asp Ile Asn Ile
340 345 350
Leu Leu Ile Gly Asp Pro Ser Val Ala Lys Ser Gln Leu Leu Arg Tyr
355 360 365
Val Leu Cys Thr Ala Pro Arg Ala Ile Pro Thr Thr Gly Arg Gly Ser
370 375 380
Ser Gly Val Gly Leu Thr Ala Ala Val Thr Thr Asp Gln Glu Thr Gly
385 390 395 400
Glu Arg Arg Leu Glu Ala Gly Ala Met Val Leu Ala Asp Arg Gly Val
405 410 415
Val Cys Ile Asp Glu Phe Asp Lys Met Ser Asp Met Asp Arg Thr Ala
420 425 430
Ile His Glu Val Met Glu Gln Gly Arg Val Thr Ile Ala Lys Ala Gly
435 440 445
Ile His Ala Arg Leu Asn Ala Arg Cys Ser Val Leu Ala Ala Ala Asn
450 455 460
Pro Val Tyr Gly Arg Tyr Asp Gln Tyr Lys Thr Pro Met Glu Asn Ile
465 470 475 480
Gly Leu Gln Asp Ser Leu Leu Ser Arg Phe Asp Leu Leu Phe Ile Met
485 490 495
Leu Asp Gln Met Asp Pro Glu Gln Asp Arg Glu Ile Ser Asp His Val
500 505 510
Leu Arg Met His Arg Tyr Arg Ala Pro Gly Glu Gln Asp Gly Asp Ala
515 520 525
Met Pro Leu Gly Ser Ala Val Asp Ile Leu Ala Thr Asp Asp Pro Asn
530 535 540
Phe Ser Gln Glu Asp Gln Gln Asp Thr Gln Ile Tyr Glu Lys His Asp
545 550 555 560
Asn Leu Leu His Gly Thr Lys Lys Lys Lys Glu Lys Met Val Ser Ala
565 570 575
Ala Phe Met Lys Lys Tyr Ile His Val Ala Lys Ile Ile Lys Pro Val
580 585 590
Leu Thr Gln Glu Ser Ala Thr Tyr Ile Ala Glu Glu Tyr Ser Arg Leu
595 600 605
Arg Ser Gln Asp Ser Met Ser Ser Asp Thr Ala Arg Thr Ser Pro Val
610 615 620
Thr Ala Arg Thr Leu Glu Thr Leu Ile Arg Leu Ala Thr Ala His Ala
625 630 635 640
Lys Ala Arg Met Ser Lys Thr Val Asp Leu Gln Asp Ala Glu Glu Ala
645 650 655
Val Glu Leu Val Gln Tyr Ala Tyr Phe Lys Lys Val Leu Glu Lys Glu
660 665 670
Lys Lys Arg Lys Lys Arg Ser Glu Asp Glu Ser Glu Thr Glu Asp Glu
675 680 685
Glu Glu Lys Ser Gln Glu Asp Gln Glu Gln Lys Arg Lys Arg Arg Lys
690 695 700
Thr Arg Gln Pro Asp Ala Lys Asp Gly Asp Ser Tyr Asp Pro Tyr Asp
705 710 715 720
Phe Ser Asp Thr Glu Glu Glu Met Pro Gln Val His Thr Pro Lys Thr
725 730 735

```
Ala Asp Ser Gln Glu Thr Lys Glu Ser Gln Lys Val Glu Leu Ser Glu
            740                 745                 750
Ser Arg Leu Lys Ala Phe Lys Val Ala Leu Leu Asp Val Phe Arg Glu
        755                 760                 765
Ala His Ala Gln Ser Ile Gly Met Asn Arg Leu Thr Glu Ser Ile Asn
    770                 775                 780
Arg Asp Ser Glu Glu Pro Phe Ser Ser Val Glu Ile Gln Ala Ala Leu
785                 790                 795                 800
Ser Lys Met Gln Asp Asp Asn Gln Val Met Val Ser Glu Gly Ile Ile
                805                 810                 815
Phe Leu Ile
```

<210> 426
<211> 178
<212> PRT
<213> Homo sapiens

<400> 426

```
Glu Pro Arg Gly Ser Arg Ala Arg Phe Gly Cys Trp Arg Leu Gln Pro
                5                  10                  15
Glu Phe Lys Pro Lys Gln Leu Glu Gly Thr Met Ala Asn Cys Glu Arg
            20                  25                  30
Thr Phe Ile Ala Ile Lys Pro Asp Gly Val Gln Arg Gly Leu Val Gly
        35                  40                  45
Glu Ile Ile Lys Arg Phe Glu Gln Lys Gly Phe Arg Leu Val Gly Leu
    50                  55                  60
Lys Phe Met Gln Ala Ser Glu Asp Leu Leu Lys Glu His Tyr Val Asp
65                  70                  75                  80
Leu Lys Asp Arg Pro Phe Phe Ala Gly Leu Val Lys Tyr Met His Ser
                85                  90                  95
Gly Pro Val Val Ala Met Val Trp Glu Gly Leu Asn Val Val Lys Thr
            100                 105                 110
Gly Arg Val Met Leu Gly Glu Thr Asn Pro Ala Asp Ser Lys Pro Gly
        115                 120                 125
Thr Ile Arg Gly Asp Phe Cys Ile Gln Val Gly Arg Asn Ile Ile His
    130                 135                 140
Gly Ser Asp Ser Val Glu Ser Ala Glu Lys Glu Ile Gly Leu Trp Phe
145                 150                 155                 160
His Pro Glu Glu Leu Val Asp Tyr Thr Ser Cys Ala Gln Asn Trp Ile
                165                 170                 175
Tyr Glu
```

<210> 427
<211> 570
<212> PRT
<213> Homo sapiens

<400> 427

```
Thr Glu Arg Ser Ala Leu Asp Val Lys Leu Lys His Ala Arg Asn Gln
                5                  10                  15
Val Asp Val Glu Ile Lys Arg Arg Gln Arg Ala Glu Ala Asp Cys Glu
            20                  25                  30
Lys Leu Glu Arg Gln Ile Gln Leu Ile Arg Glu Met Leu Met Cys Asp
        35                  40                  45
Thr Ser Gly Ser Ile Gln Leu Ser Glu Glu Gln Lys Ser Ala Leu Ala
    50                  55                  60
Phe Leu Asn Arg Gly Gln Pro Ser Ser Ser Asn Ala Gly Asn Lys Arg
```

```
 65                  70                  75                  80
Leu Ser Thr Ile Asp Glu Ser Gly Ser Ile Leu Ser Asp Ile Ser Phe
                85                  90                  95
Asp Lys Thr Asp Glu Ser Leu Asp Trp Asp Ser Ser Leu Val Lys Thr
            100                 105                 110
Phe Lys Leu Lys Lys Arg Glu Lys Arg Arg Ser Thr Ser Arg Gln Phe
        115                 120                 125
Val Asp Gly Pro Pro Gly Pro Val Lys Lys Thr Arg Ser Ile Gly Ser
    130                 135                 140
Ala Val Asp Gln Gly Asn Glu Ser Ile Val Ala Lys Thr Thr Val Thr
145                 150                 155                 160
Val Pro Asn Asp Gly Gly Pro Ile Glu Ala Val Ser Thr Ile Glu Thr
                165                 170                 175
Val Pro Tyr Trp Thr Arg Ser Arg Arg Lys Thr Gly Thr Leu Gln Pro
            180                 185                 190
Trp Asn Ser Asp Ser Thr Leu Asn Ser Arg Gln Leu Glu Pro Arg Thr
        195                 200                 205
Glu Thr Asp Ser Val Gly Thr Pro Gln Ser Asn Gly Gly Met Arg Leu
    210                 215                 220
His Asp Phe Val Ser Lys Thr Val Ile Lys Pro Glu Ser Cys Val Pro
225                 230                 235                 240
Cys Gly Lys Arg Ile Lys Phe Gly Lys Leu Ser Leu Lys Cys Arg Asp
                245                 250                 255
Cys Arg Val Val Ser His Pro Glu Cys Arg Asp Arg Cys Pro Leu Pro
            260                 265                 270
Cys Ile Pro Thr Leu Ile Gly Thr Pro Val Lys Ile Gly Glu Gly Met
        275                 280                 285
Leu Ala Asp Phe Val Ser Gln Thr Ser Pro Met Ile Pro Ser Ile Val
    290                 295                 300
Val His Cys Val Asn Glu Ile Glu Gln Arg Gly Leu Thr Glu Thr Gly
305                 310                 315                 320
Leu Tyr Arg Ile Ser Gly Cys Asp Arg Thr Val Lys Glu Leu Lys Glu
                325                 330                 335
Lys Phe Leu Arg Val Lys Thr Val Pro Leu Leu Ser Lys Val Asp Asp
            340                 345                 350
Ile His Ala Ile Cys Ser Leu Leu Lys Asp Phe Leu Arg Asn Leu Lys
        355                 360                 365
Glu Pro Leu Leu Thr Phe Arg Leu Asn Arg Ala Phe Met Glu Ala Ala
    370                 375                 380
Glu Ile Thr Asp Glu Asp Asn Ser Ile Ala Ala Met Tyr Gln Ala Val
385                 390                 395                 400
Gly Glu Leu Pro Gln Ala Asn Arg Asp Thr Leu Ala Phe Leu Met Ile
                405                 410                 415
His Leu Gln Arg Val Ala Gln Ser Pro His Thr Lys Met Asp Val Ala
            420                 425                 430
Asn Leu Ala Lys Val Phe Gly Pro Thr Ile Val Ala His Ala Val Pro
        435                 440                 445
Asn Pro Asp Pro Val Thr Met Leu Gln Asp Ile Lys Arg Gln Pro Lys
    450                 455                 460
Val Val Glu Arg Leu Leu Ser Leu Pro Leu Glu Tyr Trp Ser Gln Phe
465                 470                 475                 480
Met Met Val Glu Gln Glu Asn Ile Asp Pro Leu His Val Ile Glu Asn
                485                 490                 495
Ser Asn Ala Phe Ser Thr Pro Gln Thr Pro Asp Ile Lys Val Ser Leu
            500                 505                 510
Leu Gly Pro Val Thr Thr Pro Glu His Gln Leu Leu Lys Thr Pro Ser
        515                 520                 525
Ser Ser Ser Leu Ser Gln Arg Val Arg Ser Thr Leu Thr Lys Asn Thr
    530                 535                 540
```

```
Pro Arg Phe Gly Ser Lys Ser Lys Ser Ala Thr Asn Leu Gly Arg Gln
545                 550                 555                 560
Gly Asn Phe Phe Ala Ser Pro Met Leu Lys
                565                 570
```

<210> 428
<211> 532
<212> PRT
<213> Homo sapiens

<400> 428

```
Leu Leu Asp Ala Gly Pro Gln Phe Pro Ala Ile Gly Val Gly Ser Phe
                  5                  10                  15
Ala Arg His His His His Ser Ala Ala Ala Ala Ala Ala Ala Ala Ala
             20                  25                  30
Glu Met Gln Asp Arg Glu Leu Ser Leu Ala Ala Ala Gln Asn Gly Phe
         35                  40                  45
Val Asp Ser Ala Ala Ala His Met Gly Ala Phe Lys Leu Asn Pro Gly
     50                  55                  60
Ala His Glu Leu Ser Pro Gly Gln Ser Ser Ala Phe Thr Ser Gln Gly
 65                  70                  75                  80
Pro Gly Ala Tyr Pro Gly Ser Ala Ala Ala Ala Ala Ala Ala Ala Ala
                 85                  90                  95
Leu Gly Pro His Ala Ala His Val Gly Ser Tyr Ser Gly Pro Pro Phe
            100                 105                 110
Asn Ser Thr Arg Asp Phe Leu Phe Arg Ser Ala Arg Leu Pro Gly Thr
        115                 120                 125
Ser Ala Pro Gly Gly Gly Gln His Gly Leu Phe Gly Pro Gly Ala Gly
    130                 135                 140
Gly Leu His His Ala His Ser Asp Ala Gln Gly His Leu Leu Phe Pro
145                 150                 155                 160
Gly Leu Pro Glu Gln His Gly Pro His Gly Ser Gln Asn Val Leu Asn
                165                 170                 175
Gly Gln Met Arg Leu Gly Leu Pro Gly Glu Val Phe Gly Arg Ser Glu
            180                 185                 190
Gln Tyr Arg Gln Val Ala Ser Pro Arg Thr Asp Pro Tyr Ser Ala Ala
        195                 200                 205
Gln Leu His Asn Gln Tyr Gly Pro Met Asn Met Asn Met Gly Met Asn
    210                 215                 220
Met Ala Ala Ala Ala Ala His His His His His His His His His Pro
225                 230                 235                 240
Gly Ala Phe Phe Arg Tyr Met Arg Gln Gln Cys Ile Lys Gln Glu Leu
                245                 250                 255
Ile Cys Lys Trp Ile Asp Pro Glu Gln Leu Ser Asn Pro Lys Lys Ser
            260                 265                 270
Cys Asn Lys Thr Phe Ser Thr Met His Glu Leu Val Thr His Val Ser
        275                 280                 285
Val Glu His Val Gly Gly Pro Glu Gln Ser Asn His Val Cys Phe Trp
    290                 295                 300
Glu Glu Cys Pro Arg Glu Gly Lys Pro Phe Lys Ala Lys Tyr Lys Leu
305                 310                 315                 320
Val Asn His Ile Arg Val His Thr Gly Glu Lys Pro Phe Pro Cys Pro
                325                 330                 335
Phe Pro Gly Cys Gly Lys Val Phe Ala Arg Ser Glu Asn Leu Lys Ile
            340                 345                 350
His Lys Arg Thr His Thr Gly Glu Lys Pro Phe Gln Cys Glu Phe Glu
        355                 360                 365
Gly Cys Asp Arg Arg Phe Ala Asn Ser Ser Asp Arg Lys Lys His Met
    370                 375                 380
```

```
His Val His Thr Ser Asp Lys Pro Tyr Leu Cys Lys Met Cys Asp Lys
385                 390                 395                 400
Ser Tyr Thr His Pro Ser Ser Leu Arg Lys His Met Lys Val His Glu
                405                 410                 415
Ser Ser Pro Gln Gly Ser Glu Ser Ser Pro Ala Ala Ser Ser Gly Tyr
            420                 425                 430
Glu Ser Ser Thr Pro Pro Gly Leu Val Ser Pro Ser Ala Glu Pro Gln
        435                 440                 445
Ser Ser Ser Asn Leu Ser Pro Ala Ala Ala Ala Ala Ala Ala Ala Ala
    450                 455                 460
Ala Ala Ala Ala Ala Ala Val Ser Ala Val His Arg Gly Gly Gly Ser
465                 470                 475                 480
Gly Ser Gly Gly Ala Gly Gly Gly Ser Gly Gly Gly Ser Gly Ser Gly
                485                 490                 495
Gly Gly Gly Gly Gly Ala Gly Gly Gly Gly Gly Gly Ser Ser Gly Gly
            500                 505                 510
Gly Ser Gly Thr Ala Gly Gly His Ser Gly Leu Ser Ser Asn Phe Asn
        515                 520                 525
Glu Trp Tyr Val
    530
```

<210> 429
<211> 629
<212> PRT
<213> Homo sapiens

<400> 429

```
Gly Gly Ala Pro Ala Ser Phe Pro Gly Arg Ala Pro Arg Ser Leu Ala
                5                   10                  15
Ser Gln Pro Ala Ala Arg Ala Ala Ala Ala Pro Ala Met Pro Ser Ala
            20                  25                  30
Lys Gln Arg Gly Ser Lys Gly Gly His Gly Ala Ala Ser Pro Ser Glu
        35                  40                  45
Lys Gly Ala His Pro Ser Gly Gly Ala Asp Asp Val Ala Lys Lys Pro
    50                  55                  60
Pro Pro Ala Pro Gln Gln Pro Pro Pro Pro Pro Ala Pro His Pro Gln
65                  70                  75                  80
Gln His Pro Gln Gln His Pro Gln Asn Gln Ala His Gly Lys Gly Gly
                85                  90                  95
His Arg Gly Gly Gly Gly Gly Gly Gly Lys Ser Ser Ser Ser Ser Ser
            100                 105                 110
Ala Ser Ala Ala Ala Ala Ala Ala Ala Ala Ser Ser Ser Ala Ser Cys
        115                 120                 125
Ser Arg Arg Leu Gly Arg Ala Leu Asn Phe Leu Phe Tyr Leu Ala Leu
    130                 135                 140
Val Ala Ala Ala Ala Phe Ser Gly Trp Cys Val His His Val Leu Glu
145                 150                 155                 160
Glu Val Gln Gln Val Arg Arg Ser His Gln Asp Phe Ser Arg Gln Arg
                165                 170                 175
Glu Glu Leu Gly Gln Gly Leu Gln Gly Val Glu Gln Lys Val Gln Ser
            180                 185                 190
Leu Gln Ala Thr Phe Gly Thr Phe Glu Ser Ile Leu Arg Ser Ser Gln
        195                 200                 205
His Lys Gln Asp Leu Thr Glu Lys Ala Val Lys Gln Gly Glu Ser Glu
    210                 215                 220
Val Ser Arg Ile Ser Glu Val Leu Gln Lys Leu Gln Asn Glu Ile Leu
225                 230                 235                 240
Lys Asp Leu Ser Asp Gly Ile His Val Val Lys Asp Ala Arg Glu Arg
```

245 250 255
Asp Phe Thr Ser Leu Glu Asn Thr Val Glu Glu Arg Leu Thr Glu Leu
260 265 270
Thr Lys Ser Ile Asn Asp Asn Ile Ala Ile Phe Thr Glu Val Gln Lys
275 280 285
Arg Ser Gln Lys Glu Ile Asn Asp Met Lys Ala Lys Val Ala Ser Leu
290 295 300
Glu Glu Ser Glu Gly Asn Lys Gln Asp Leu Lys Ala Leu Lys Glu Ala
305 310 315 320
Val Lys Glu Ile Gln Thr Ser Ala Lys Ser Arg Glu Trp Asp Met Glu
325 330 335
Ala Leu Arg Ser Thr Leu Gln Thr Met Glu Ser Asp Ile Tyr Thr Glu
340 345 350
Val Arg Glu Leu Val Ser Leu Lys Gln Glu Gln Gln Ala Phe Lys Glu
355 360 365
Ala Ala Asp Thr Glu Arg Leu Ala Leu Gln Ala Leu Thr Glu Lys Leu
370 375 380
Leu Arg Ser Glu Glu Ser Val Ser Arg Leu Pro Glu Glu Ile Arg Arg
385 390 395 400
Leu Glu Glu Glu Leu Arg Gln Leu Lys Ser Asp Ser His Gly Pro Lys
405 410 415
Glu Asp Gly Gly Phe Arg His Ser Glu Ala Phe Glu Ala Leu Gln Gln
420 425 430
Lys Ser Gln Gly Leu Asp Ser Arg Leu Gln His Val Glu Asp Gly Val
435 440 445
Leu Ser Met Gln Val Ala Ser Ala Arg Gln Thr Glu Ser Leu Glu Ser
450 455 460
Leu Leu Ser Lys Ser Gln Glu His Glu Gln Arg Leu Ala Pro Ala Gly
465 470 475 480
Ala Leu Glu Gly Leu Gly Ser Ser Glu Ala Asp Gln Asp Gly Leu Ala
485 490 495
Ser Thr Val Arg Ser Leu Gly Glu Thr Gln Leu Val Leu Tyr Gly Asp
500 505 510
Val Glu Glu Leu Lys Arg Ser Val Gly Glu Leu Pro Ser Thr Val Glu
515 520 525
Ser Leu Gln Lys Val Gln Glu Gln Val His Thr Leu Leu Ser Gln Asp
530 535 540
Gln Ala Gln Ala Ala Arg Leu Pro Pro Gln Asp Phe Leu Asp Arg Leu
545 550 555 560
Ser Ser Leu Asp Asn Leu Lys Ala Ser Val Ser Gln Val Glu Ala Asp
565 570 575
Leu Lys Met Leu Arg Thr Ala Val Asp Ser Leu Val Ala Tyr Ser Val
580 585 590
Lys Ile Glu Thr Asn Glu Asn Asn Leu Glu Ser Ala Lys Gly Leu Leu
595 600 605
Asp Asp Leu Arg Asn Asp Leu Asp Arg Leu Phe Val Lys Val Glu Lys
610 615 620
Ile His Glu Lys Val
625

<210> 430
<211> 147
<212> PRT
<213> Homo sapiens

<400> 430
Pro Gln Trp Cys Pro Arg Ser Gln Ala Arg Ser Ser Ala Ala Ala Ala
5 10 15

```
Ala Arg Ala Ser Val Pro Leu Arg Gly Ser Pro Gly Pro Ser Ala Ile
            20                  25                  30
Met Pro Met Phe Ile Val Asn Thr Asn Val Pro Arg Ala Ser Val Pro
        35                  40                  45
Asp Gly Phe Leu Ser Glu Leu Thr Gln Gln Leu Ala Gln Ala Thr Gly
    50                  55                  60
Lys Pro Pro Gln Tyr Ile Ala Val His Val Val Pro Asp Gln Leu Met
65                  70                  75                  80
Ala Phe Gly Gly Ser Ser Glu Pro Cys Ala Leu Cys Ser Leu His Ser
                85                  90                  95
Ile Gly Lys Ile Gly Gly Ala Gln Asn Arg Ser Tyr Ser Lys Leu Leu
            100                 105                 110
Cys Gly Leu Leu Ala Glu Arg Leu Arg Ile Ser Pro Asp Arg Val Tyr
        115                 120                 125
Ile Asn Tyr Tyr Asp Met Asn Ala Ala Asn Val Gly Trp Asn Asn Ser
    130                 135                 140
Thr Phe Ala
145
```

<210> 431
<211> 775
<212> PRT
<213> Homo sapiens

<400> 431

```
Leu Ala Pro Pro Arg Gln Leu Glu Ser Thr Ser Ser Ala Val Arg Leu
                5                   10                  15
Thr Glu Met Leu Arg Ala Cys Gln Leu Ser Gly Val Thr Ala Ala Ala
            20                  25                  30
Gln Ser Cys Leu Cys Gly Lys Phe Val Leu Arg Pro Leu Arg Pro Cys
        35                  40                  45
Arg Arg Tyr Ser Thr Ser Gly Ser Ser Gly Leu Thr Thr Gly Lys Ile
    50                  55                  60
Ala Gly Ala Gly Leu Leu Phe Val Gly Gly Gly Ile Gly Gly Thr Ile
65                  70                  75                  80
Leu Tyr Ala Lys Trp Asp Ser His Phe Arg Glu Ser Val Glu Lys Thr
                85                  90                  95
Ile Pro Tyr Ser Asp Lys Leu Phe Glu Met Val Leu Gly Pro Ala Ala
            100                 105                 110
Tyr Asn Val Pro Leu Pro Lys Lys Ser Ile Gln Ser Gly Pro Leu Lys
        115                 120                 125
Ile Ser Ser Val Ser Glu Val Met Lys Glu Ser Lys Gln Pro Ala Ser
    130                 135                 140
Gln Leu Gln Lys Gln Lys Gly Asp Thr Pro Ala Ser Ala Thr Ala Pro
145                 150                 155                 160
Thr Glu Ala Ala Gln Ile Ile Ser Ala Ala Gly Asp Thr Leu Ser Val
                165                 170                 175
Pro Ala Pro Ala Val Gln Pro Glu Glu Ser Leu Lys Thr Asp His Pro
            180                 185                 190
Glu Ile Gly Glu Gly Lys Pro Thr Pro Ala Leu Ser Glu Glu Ala Ser
        195                 200                 205
Ser Ser Ser Ile Arg Glu Arg Pro Pro Glu Glu Val Ala Ala Arg Leu
    210                 215                 220
Ala Gln Gln Glu Lys Gln Glu Gln Val Lys Ile Glu Ser Leu Ala Lys
225                 230                 235                 240
Ser Leu Glu Asp Ala Leu Arg Gln Thr Ala Ser Val Thr Leu Gln Ala
                245                 250                 255
Ile Ala Ala Gln Asn Ala Ala Val Gln Ala Val Asn Ala His Ser Asn
```

```
                260                 265                 270
Ile Leu Lys Ala Ala Met Asp Asn Ser Glu Ile Ala Gly Glu Lys Lys
        275                 280                 285
Ser Ala Gln Trp Arg Thr Val Glu Gly Ala Leu Lys Glu Arg Arg Lys
    290                 295                 300
Ala Val Asp Glu Ala Ala Asp Ala Leu Leu Lys Ala Lys Glu Glu Leu
305                 310                 315                 320
Glu Lys Met Lys Ser Val Ile Glu Asn Ala Lys Lys Lys Glu Val Ala
                325                 330                 335
Gly Ala Lys Pro His Ile Thr Ala Ala Glu Gly Lys Leu His Asn Met
            340                 345                 350
Ile Val Asp Leu Asp Asn Val Val Lys Lys Val Gln Ala Ala Gln Ser
        355                 360                 365
Glu Ala Lys Val Val Ser Gln Tyr His Glu Leu Val Val Gln Ala Arg
    370                 375                 380
Asp Asp Phe Lys Arg Glu Leu Asp Ser Ile Thr Pro Glu Val Leu Pro
385                 390                 395                 400
Gly Trp Lys Gly Met Ser Val Ser Asp Leu Ala Asp Lys Leu Ser Thr
                405                 410                 415
Asp Asp Leu Asn Ser Leu Ile Ala His Ala His Arg Arg Ile Asp Gln
            420                 425                 430
Leu Asn Arg Glu Leu Ala Glu Gln Lys Ala Thr Glu Lys Gln His Ile
        435                 440                 445
Thr Leu Ala Leu Glu Lys Gln Lys Leu Glu Glu Lys Arg Ala Phe Asp
    450                 455                 460
Ser Ala Val Ala Lys Ala Leu Glu His His Arg Ser Glu Ile Gln Ala
465                 470                 475                 480
Glu Gln Asp Arg Lys Ile Glu Glu Val Arg Asp Ala Met Glu Asn Glu
                485                 490                 495
Met Arg Thr Gln Leu Arg Arg Gln Ala Ala Ala His Thr Asp His Leu
            500                 505                 510
Arg Asp Val Leu Arg Val Gln Glu Gln Glu Leu Lys Ser Glu Phe Glu
        515                 520                 525
Gln Asn Leu Ser Glu Lys Leu Ser Glu Gln Glu Leu Gln Phe Arg Arg
    530                 535                 540
Leu Ser Gln Glu Gln Val Asp Asn Phe Thr Leu Asp Ile Asn Thr Ala
545                 550                 555                 560
Tyr Ala Arg Leu Arg Gly Ile Glu Gln Ala Val Gln Ser His Ala Val
                565                 570                 575
Ala Glu Glu Glu Ala Arg Lys Ala His Gln Leu Trp Leu Ser Val Glu
            580                 585                 590
Ala Leu Lys Tyr Ser Met Lys Thr Ser Ser Ala Glu Thr Pro Thr Ile
        595                 600                 605
Pro Leu Gly Ser Ala Val Glu Ala Ile Lys Ala Asn Cys Ser Asp Asn
    610                 615                 620
Glu Phe Thr Gln Ala Leu Thr Ala Ala Ile Pro Pro Glu Ser Leu Thr
625                 630                 635                 640
Arg Gly Val Tyr Ser Glu Glu Thr Leu Arg Ala Arg Phe Tyr Ala Val
                645                 650                 655
Gln Lys Leu Ala Arg Arg Val Ala Met Ile Asp Glu Thr Arg Asn Ser
            660                 665                 670
Leu Tyr Gln Tyr Phe Leu Ser Tyr Leu Gln Ser Leu Leu Leu Phe Pro
        675                 680                 685
Pro Gln Gln Leu Lys Pro Pro Pro Glu Leu Cys Pro Glu Asp Ile Asn
    690                 695                 700
Thr Phe Lys Leu Leu Ser Tyr Ala Ser Tyr Cys Ile Glu His Gly Asp
705                 710                 715                 720
Leu Glu Leu Ala Ala Lys Phe Val Asn Gln Leu Lys Gly Glu Ser Arg
                725                 730                 735
```

```
Arg Val Ala Gln Asp Trp Leu Lys Glu Ala Arg Met Thr Leu Glu Thr
            740                 745                 750
Lys Gln Ile Val Glu Ile Leu Thr Ala Tyr Ala Ser Ala Val Gly Ile
        755                 760                 765
Gly Thr Thr Gln Val Gln Pro
    770                 775
```

<210> 432
<211> 741
<212> PRT
<213> Homo sapiens

<400> 432

```
Arg Pro Lys Arg Leu Arg Thr Gly Asn Met Val Arg Ser Gly Asn Lys
                5                  10                  15
Ala Ala Val Val Leu Cys Met Asp Val Gly Phe Thr Met Ser Asn Ser
            20                  25                  30
Ile Pro Gly Ile Glu Ser Pro Phe Glu Gln Ala Lys Lys Val Ile Thr
        35                  40                  45
Met Phe Val Gln Arg Gln Val Phe Ala Glu Asn Lys Asp Glu Ile Ala
    50                  55                  60
Leu Val Leu Phe Gly Thr Asp Gly Thr Asp Asn Pro Leu Ser Gly Gly
65                  70                  75                  80
Asp Gln Tyr Gln Asn Ile Thr Val His Arg His Leu Met Leu Pro Asp
                85                  90                  95
Phe Asp Leu Leu Glu Asp Ile Glu Ser Lys Ile Gln Pro Gly Ser Gln
            100                 105                 110
Gln Ala Asp Phe Leu Asp Ala Leu Ile Val Ser Met Asp Val Ile Gln
        115                 120                 125
His Glu Thr Ile Gly Lys Lys Phe Glu Lys Arg His Ile Glu Ile Phe
    130                 135                 140
Thr Asp Leu Ser Ser Arg Phe Ser Lys Ser Gln Leu Asp Ile Ile Ile
145                 150                 155                 160
His Ser Leu Lys Lys Cys Asp Ile Ser Leu Gln Phe Phe Leu Pro Phe
                165                 170                 175
Ser Leu Gly Lys Glu Asp Gly Ser Gly Asp Arg Gly Asp Gly Pro Phe
            180                 185                 190
Arg Leu Gly Gly His Gly Pro Ser Phe Pro Leu Lys Gly Ile Thr Glu
        195                 200                 205
Gln Gln Lys Glu Gly Leu Glu Ile Val Lys Met Val Met Ile Ser Leu
    210                 215                 220
Glu Gly Glu Asp Gly Leu Asp Glu Ile Tyr Ser Phe Ser Glu Ser Leu
225                 230                 235                 240
Arg Lys Leu Cys Val Phe Lys Lys Ile Glu Arg His Ser Ile His Trp
                245                 250                 255
Pro Cys Arg Leu Thr Ile Gly Ser Asn Leu Ser Ile Arg Ile Ala Ala
            260                 265                 270
Tyr Lys Ser Ile Leu Gln Glu Arg Val Lys Lys Thr Trp Thr Val Val
        275                 280                 285
Asp Ala Lys Thr Leu Lys Lys Glu Asp Ile Gln Lys Glu Thr Val Tyr
    290                 295                 300
Cys Leu Asn Asp Asp Asp Glu Thr Glu Val Leu Lys Glu Asp Ile Ile
305                 310                 315                 320
Gln Gly Phe Arg Tyr Gly Ser Asp Ile Val Pro Phe Ser Lys Val Asp
                325                 330                 335
Glu Glu Gln Met Lys Tyr Lys Ser Glu Gly Lys Cys Phe Ser Val Leu
            340                 345                 350
Gly Phe Cys Lys Ser Ser Gln Val Gln Arg Arg Phe Phe Met Gly Asn
```

```
        355                 360                 365
Gln Val Leu Lys Val Phe Ala Ala Arg Asp Asp Glu Ala Ala Ala Val
    370                 375                 380
Ala Leu Ser Ser Leu Ile His Ala Leu Asp Asp Leu Asp Met Val Ala
385                 390                 395                 400
Ile Val Arg Tyr Ala Tyr Asp Lys Arg Ala Asn Pro Gln Val Gly Val
                405                 410                 415
Ala Phe Pro His Ile Lys His Asn Tyr Glu Cys Leu Val Tyr Val Gln
            420                 425                 430
Leu Pro Phe Met Glu Asp Leu Arg Gln Tyr Met Phe Ser Ser Leu Lys
        435                 440                 445
Asn Ser Lys Lys Tyr Ala Pro Thr Glu Ala Gln Leu Asn Ala Val Asp
    450                 455                 460
Ala Leu Ile Asp Ser Met Ser Leu Ala Lys Lys Asp Glu Lys Thr Asp
465                 470                 475                 480
Thr Leu Glu Asp Leu Phe Pro Thr Thr Lys Ile Pro Asn Pro Arg Phe
                485                 490                 495
Gln Arg Leu Phe Gln Cys Leu Leu His Arg Ala Leu His Pro Arg Glu
            500                 505                 510
Pro Leu Pro Pro Ile Gln Gln His Ile Trp Asn Met Leu Asn Pro Pro
        515                 520                 525
Ala Glu Val Thr Thr Lys Ser Gln Ile Pro Leu Ser Lys Ile Lys Thr
    530                 535                 540
Leu Phe Pro Leu Ile Glu Ala Lys Lys Lys Asp Gln Val Thr Ala Gln
545                 550                 555                 560
Glu Ile Phe Gln Asp Asn His Glu Asp Gly Pro Thr Ala Lys Lys Leu
                565                 570                 575
Lys Thr Glu Gln Gly Gly Ala His Phe Ser Val Ser Ser Leu Ala Glu
            580                 585                 590
Gly Ser Val Thr Ser Val Gly Ser Val Asn Pro Ala Glu Asn Phe Arg
        595                 600                 605
Val Leu Val Lys Gln Lys Lys Ala Ser Phe Glu Glu Ala Ser Asn Gln
    610                 615                 620
Leu Ile Asn His Ile Glu Gln Phe Leu Asp Thr Asn Glu Thr Pro Tyr
625                 630                 635                 640
Phe Met Lys Ser Ile Asp Cys Ile Arg Ala Phe Arg Glu Glu Ala Ile
                645                 650                 655
Lys Phe Ser Glu Glu Gln Arg Phe Asn Asn Phe Leu Lys Ala Leu Gln
            660                 665                 670
Glu Lys Val Glu Ile Lys Gln Leu Asn His Phe Trp Glu Ile Val Val
        675                 680                 685
Gln Asp Gly Ile Thr Leu Ile Thr Lys Glu Glu Ala Ser Gly Ser Ser
    690                 695                 700
Val Thr Ala Glu Glu Ala Lys Lys Phe Leu Ala Pro Lys Asp Lys Pro
705                 710                 715                 720
Ser Gly Asp Thr Ala Ala Val Phe Glu Glu Gly Gly Asp Val Asp Asp
                725                 730                 735
Leu Leu Asp Met Ile
            740
```

<210> 433
<211> 291
<212> PRT
<213> Homo sapiens

<400> 433

```
Phe Arg Pro Arg Tyr Glu Gly Arg Gly Arg Gly Cys Cys Gly Arg Val
 -                5                  10                  15
```

```
Leu Leu Leu Arg Arg Gly Leu His Val Asp Cys Gly Lys Leu Gly Asn
            20                  25                  30
Lys Leu Thr Ser Ser Cys Gly Lys Pro Ser Ser Asn Arg Met Ser Leu
        35                  40                  45
Gln Trp Thr Ala Val Ala Thr Phe Leu Tyr Ala Glu Val Phe Val Val
    50                  55                  60
Leu Leu Leu Cys Ile Pro Phe Ile Ser Pro Lys Arg Trp Gln Lys Ile
65                  70                  75                  80
Phe Lys Ser Arg Leu Val Glu Leu Leu Val Ser Tyr Gly Asn Thr Phe
                85                  90                  95
Phe Val Val Leu Ile Val Ile Leu Val Leu Leu Val Ile Asp Ala Val
            100                 105                 110
Arg Glu Ile Arg Lys Tyr Asp Asp Val Thr Glu Lys Val Asn Leu Gln
        115                 120                 125
Asn Asn Pro Gly Ala Met Glu His Phe His Met Lys Leu Phe Arg Ala
    130                 135                 140
Gln Arg Asn Leu Tyr Ile Ala Gly Phe Ser Leu Leu Leu Ser Phe Leu
145                 150                 155                 160
Leu Arg Arg Leu Val Thr Leu Ile Ser Gln Gln Ala Thr Leu Leu Ala
                165                 170                 175
Ser Asn Glu Ala Phe Lys Lys Gln Ala Glu Ser Ala Ser Glu Ala Ala
            180                 185                 190
Lys Lys Tyr Met Glu Glu Asn Asp Gln Leu Lys Lys Gly Ala Ala Val
        195                 200                 205
Asp Gly Gly Lys Leu Asp Val Gly Asn Ala Glu Val Lys Leu Glu Glu
    210                 215                 220
Glu Asn Arg Ser Leu Lys Ala Asp Leu Gln Lys Leu Lys Asp Glu Leu
225                 230                 235                 240
Ala Ser Thr Lys Gln Lys Leu Glu Lys Ala Glu Asn Gln Val Leu Ala
                245                 250                 255
Met Arg Lys Gln Ser Glu Gly Leu Thr Lys Glu Tyr Asp Arg Leu Leu
            260                 265                 270
Glu Glu His Ala Lys Leu Gln Ala Ala Val Asp Gly Pro Met Asp Lys
        275                 280                 285
Lys Glu Glu
    290
```

<210> 434
<211> 349
<212> PRT
<213> *Homo sapiens*

<400> 434

```
Gly Val Ala Pro Trp Gly Arg Gly Arg Ala Ala Pro Arg Cys Ala Ser
                5                   10                  15
Ala Thr Val Gly Gly Ser Gly Ile Gly Arg Leu Arg Gly Ile Thr Ser
            20                  25                  30
Ser Gly Leu Lys Met Asp Asn Lys Lys Arg Leu Ala Tyr Ala Ile Ile
        35                  40                  45
Gln Phe Leu His Asp Gln Leu Arg His Gly Gly Leu Ser Ser Asp Ala
    50                  55                  60
Gln Glu Ser Leu Glu Val Ala Ile Gln Cys Leu Glu Thr Ala Phe Gly
65                  70                  75                  80
Val Thr Val Glu Asp Ser Asp Leu Ala Leu Pro Gln Thr Leu Pro Glu
                85                  90                  95
Ile Phe Glu Ala Ala Ala Thr Gly Lys Glu Met Pro Gln Asp Leu Arg
            100                 105                 110
Ser Pro Ala Arg Thr Pro Pro Ser Glu Glu Asp Ser Ala Glu Ala Glu
```

```
         115                 120                 125
Arg Leu Lys Thr Glu Gly Asn Glu Gln Met Lys Val Glu Asn Phe Glu
    130                 135                 140
Ala Ala Val His Phe Tyr Gly Lys Ala Ile Glu Leu Asn Pro Ala Asn
145                 150                 155                 160
Ala Val Tyr Phe Cys Asn Arg Ala Ala Ala Tyr Ser Lys Leu Gly Asn
                165                 170                 175
Tyr Ala Gly Ala Val Gln Asp Cys Glu Arg Ala Ile Cys Ile Asp Pro
            180                 185                 190
Ala Tyr Ser Lys Ala Tyr Gly Arg Met Gly Leu Ala Leu Ser Ser Leu
        195                 200                 205
Asn Lys His Val Glu Ala Val Ala Tyr Tyr Lys Lys Ala Leu Glu Leu
    210                 215                 220
Asp Pro Asp Asn Glu Thr Tyr Lys Ser Asn Leu Lys Ile Ala Glu Leu
225                 230                 235                 240
Lys Leu Arg Glu Ala Pro Ser Pro Thr Gly Gly Val Gly Ser Phe Asp
                245                 250                 255
Ile Ala Gly Leu Leu Asn Asn Pro Gly Phe Met Ser Met Ala Ser Asn
            260                 265                 270
Leu Met Asn Asn Pro Gln Ile Gln Gln Leu Met Ser Gly Met Ile Ser
        275                 280                 285
Gly Gly Asn Asn Pro Leu Gly Thr Pro Gly Thr Ser Pro Ser Gln Asn
    290                 295                 300
Asp Leu Ala Ser Leu Ile Gln Ala Gly Gln Gln Phe Ala Gln Gln Met
305                 310                 315                 320
Gln Gln Gln Asn Pro Glu Leu Ile Glu Gln Leu Arg Ser Gln Ile Arg
                325                 330                 335
Ser Arg Thr Pro Ser Ala Ser Asn Asp Asp Gln Gln Glu
            340                 345
```

<210> 435
<211> 519
<212> PRT
<213> Homo sapiens

<400> 435

```
Gln Pro Ser Ala Glu Pro Arg Arg Thr Met Pro Ala Val Asp Lys Leu
                5                   10                  15
Leu Leu Glu Glu Ala Leu Gln Asp Ser Pro Gln Thr Arg Ser Leu Leu
            20                  25                  30
Ser Val Phe Glu Glu Asp Ala Gly Thr Leu Thr Asp Tyr Thr Asn Gln
        35                  40                  45
Leu Leu Gln Ala Met Gln Arg Val Tyr Gly Ala Gln Asn Glu Met Cys
    50                  55                  60
Leu Ala Thr Gln Gln Leu Ser Lys Gln Leu Leu Ala Tyr Glu Lys Gln
65                  70                  75                  80
Asn Phe Ala Leu Gly Lys Gly Asp Glu Glu Val Ile Ser Thr Leu His
                85                  90                  95
Tyr Phe Ser Lys Val Val Asp Glu Leu Asn Leu Leu His Thr Glu Leu
            100                 105                 110
Ala Lys Gln Leu Ala Asp Thr Met Val Leu Pro Ile Ile Gln Phe Arg
        115                 120                 125
Glu Lys Asp Leu Thr Glu Val Ser Thr Leu Lys Asp Leu Phe Gly Leu
    130                 135                 140
Ala Ser Asn Glu His Asp Leu Ser Met Ala Lys Tyr Ser Arg Leu Pro
145                 150                 155                 160
Lys Lys Lys Glu Asn Glu Lys Val Lys Thr Glu Val Gly Lys Glu Val
                165                 170                 175
```

```
Ala Ala Ala Arg Arg Lys Gln His Leu Ser Ser Leu Gln Tyr Tyr Cys
            180                 185                 190
Ala Leu Asn Ala Leu Gln Tyr Arg Lys Gln Met Ala Met Met Glu Pro
        195                 200                 205
Met Ile Gly Phe Ala His Gly Gln Ile Asn Phe Phe Lys Lys Gly Ala
    210                 215                 220
Glu Met Phe Ser Lys Arg Met Asp Ser Phe Leu Ser Ser Val Ala Asp
225                 230                 235                 240
Met Val Gln Ser Ile Gln Val Glu Leu Glu Ala Glu Ala Glu Lys Met
                245                 250                 255
Arg Val Ser Gln Gln Glu Leu Leu Ser Val Asp Glu Ser Val Tyr Thr
            260                 265                 270
Pro Asp Ser Asp Val Ala Ala Pro Gln Ile Asn Arg Asn Leu Ile Gln
        275                 280                 285
Lys Ala Gly Tyr Leu Asn Leu Arg Asn Lys Thr Gly Leu Val Thr Thr
    290                 295                 300
Thr Trp Glu Arg Leu Tyr Phe Phe Thr Gln Gly Gly Asn Leu Met Cys
305                 310                 315                 320
Gln Pro Arg Gly Ala Val Ala Gly Gly Leu Ile Gln Asp Leu Asp Asn
                325                 330                 335
Cys Ser Val Met Ala Val Asp Cys Glu Asp Arg Arg Tyr Cys Phe Gln
            340                 345                 350
Ile Thr Thr Pro Asn Gly Lys Ser Gly Ile Ile Leu Gln Ala Glu Ser
        355                 360                 365
Arg Lys Glu Asn Glu Glu Trp Ile Cys Ala Ile Asn Asn Thr Ser Arg
    370                 375                 380
Gln Ile Tyr Leu Thr Asp Asn Pro Glu Ala Val Ala Ile Lys Leu Asn
385                 390                 395                 400
Gln Thr Ala Leu Gln Ala Val Thr Pro Ile Thr Ser Phe Gly Lys Lys
                405                 410                 415
Gln Glu Ser Ser Cys Pro Ser Gln Asn Leu Lys Asn Ser Glu Met Glu
            420                 425                 430
Asn Glu Asn Asp Lys Ile Val Pro Lys Ala Thr Ala Ser Leu Pro Glu
        435                 440                 445
Ala Glu Glu Leu Ile Ala Pro Gly Thr Pro Ile Gln Phe Asp Ile Val
    450                 455                 460
Leu Pro Ala Thr Glu Phe Leu Asp Gln Asn Arg Gly Ser Arg Arg Thr
465                 470                 475                 480
Asn Pro Phe Gly Glu Thr Glu Asp Glu Ser Phe Pro Glu Ala Glu Asp
                485                 490                 495
Ser Leu Leu Gln Gln Met Phe Ile Val Arg Phe Leu Gly Ser Met Ala
            500                 505                 510
Val Lys Thr Asp Ser Thr Thr
        515
```

<210> 436
<211> 357
<212> PRT
<213> Homo sapiens

<400> 436

```
Met Leu Gln Ile His Leu Pro Gly Arg His Thr Leu Phe Val Arg Ala
                5                   10                  15
Met Ile Asp Ser Gly Ala Ser Gly Asn Phe Ile Asp His Glu Tyr Val
            20                  25                  30
Ala Gln Asn Gly Ile Pro Leu Arg Ile Lys Asp Trp Pro Ile Leu Val
        35                  40                  45
Glu Ala Ile Asp Gly Arg Pro Ile Ala Ser Gly Pro Val Val His Glu
```

```
     50                  55                  60
Thr His Asp Leu Ile Val Asp Leu Gly Asp His Arg Glu Val Leu Ser
 65                  70                  75                  80
Phe Asp Val Thr Gln Ser Pro Phe Phe Pro Val Val Leu Gly Val Arg
                 85                  90                  95
Trp Leu Ser Thr His Asp Pro Asn Ile Thr Trp Ser Thr Arg Ser Ile
            100                 105                 110
Val Phe Asp Ser Glu Tyr Cys Arg Tyr His Cys Arg Met Tyr Ser Pro
        115                 120                 125
Ile Pro Pro Ser Leu Pro Pro Pro Ala Pro Gln Pro Pro Leu Tyr Tyr
    130                 135                 140
Pro Val Asp Gly Tyr Arg Val Tyr Gln Pro Val Arg Tyr Tyr Tyr Val
145                 150                 155                 160
Gln Asn Val Tyr Thr Pro Val Asp Glu His Val Tyr Pro Asp His Arg
                165                 170                 175
Leu Val Asp Pro His Ile Glu Met Ile Pro Gly Ala His Ser Ile Pro
            180                 185                 190
Ser Gly His Val Tyr Ser Leu Ser Glu Pro Glu Met Ala Ala Leu Arg
        195                 200                 205
Asp Phe Val Ala Arg Asn Val Lys Asp Gly Leu Ile Thr Pro Thr Ile
    210                 215                 220
Ala Pro Asn Gly Ala Gln Val Leu Gln Val Lys Arg Gly Trp Lys Leu
225                 230                 235                 240
Gln Val Ser Tyr Asp Cys Arg Ala Pro Asn Asn Phe Thr Ile Gln Asn
                245                 250                 255
Gln Tyr Pro Arg Leu Ser Ile Pro Asn Leu Glu Asp Gln Ala His Leu
            260                 265                 270
Ala Thr Tyr Thr Glu Phe Val Pro Gln Ile Pro Gly Tyr Gln Thr Tyr
        275                 280                 285
Pro Thr Tyr Ala Ala Tyr Pro Thr Tyr Pro Val Gly Phe Ala Trp Tyr
    290                 295                 300
Pro Val Gly Arg Asp Gly Gln Gly Arg Ser Leu Tyr Val Pro Val Met
305                 310                 315                 320
Ile Thr Trp Asn Pro His Trp Tyr Arg Gln Pro Pro Val Pro Gln Tyr
                325                 330                 335
Pro Pro Pro Gln Pro Pro Pro Pro Pro Pro Pro Pro Pro Pro Pro Pro
            340                 345                 350
Ser Tyr Ser Thr Leu
        355
```

<210> 437
<211> 501
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(501)
<223> n = A,T,C or G

<400> 437
cgcaccagct ctctgctctc ccagcgcagc gccgccgccc ggcccctcca gcttcccgga 60
ccatggccaa cctggagcgc accttcatcg ccatcaagcc ggacggcgtg cagcgcggcc 120
tggtgggcga gatcatcaag cgcttcgagc agaagggatt ccgcctcgtg gccatgaagt 180
tcctccgggc ctctgaagaa cacctgaagc agcactacat tgacctgaaa gaccgaccat 240
tcttccctgg gctggtgaag tacatgaact cagggccggt tgtggccatg gtctgggagg 300
ggctgaacgt ggtgaagaca ggccgagtga tgcttgggga gaccaatcca gcagattcaa 360

agccaggcac cattcgtggg gacttctgca ttcaggttgg caggaacatc attcatggca 420
gtgattcagt aaaaagtgct gaaaaagaaa tcancctatg gtttaagcct gaanaactgg 480
ttgactacaa gtcttgtgct c 501

<210> 438
<211> 501
<212> DNA
<213> Homo sapiens

<400> 438
tgaaatactg gagctgttgt agaagaaaaa cttctgattt taatacattc ttagcccaag 60
agggctgtac aaaagggaaa cacatgtgga ctaaaaaaga tgctgggaaa aaagttgttc 120
catgtagaca tgactggcat cagactggag ggtgaaagtt ccatttcagt atatgctaaa 180
aactcacttc cagaacttag ccgagtagaa gcaaatagca cattgttaaa tgtgcatatt 240
gtatttgaag gagagaagga atttgatcaa aatgtgaaat tatggggtgt gattgatgta 300
aagcgaagtt atgtaactat gactgcaaca aagattgaaa tcactatgag aaaagctgaa 360
ccgatgcagt gggcaagcct tgaactgcct gcagctaaaa agcaggaaaa acaaaaagat 420
gacacaacag attgagtggg agatggaagg aaggctatta cattatttcc gaatttttaa 480
tactgtgtga agtggtgggc t 501

<210> 439
<211> 501
<212> DNA
<213> Homo sapiens

<400> 439
taaaacaagc acttgataaa cttaaactgt catcagggaa tgaagaaaat aagaaagaag 60
aagacaatga tgaaattaag attgggacct catgtaagaa tggagggtgt tcaaagacat 120
accagggtct agagagtcta gaagaagtct gtgtatatca ttctggagta cctattttcc 180
atgaggggat gaaatactgg agctgttgta gaagaaaaac ttctgatttt aatacattct 240
tagcccaaga gggctgtaca aaagggaaac acatgtggac taaaaaagat gctgggaaaa 300
aagttgttcc atgtagacat gactggcatc agactggagg tgaagttacc atttcagtat 360
atgctaaaaa ctcacttcca gaacttagcc cgagtagaag caaatagcac attgttaaat 420
gtgcatattg tatttgaagg agagaaggaa tttgatcaaa atgtgaaatt atggggtgtg 480
attgatgtaa agcgaattat t 501

<210> 440
<211> 481
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(481)
<223> n = A,T,C or G

<400> 440
tgatccctat tgttttgtgg agtttcatga gcatcgtcat gcagctgcag cattagctgc 60
tatgaatgga cggaagataa tgggtaagga agtcaaagtg aattgggcaa caacccctag 120
cagtcaaaag aaagatacaa gcaatcattt ccatgtcttt gttggtgatc tcagcccaga 180
aattacaact gaagatataa aagctgcttt tgcaccattt ggaagaatat cagatgcccg 240
agtggtaaaa gacatggcaa caggaaagtc taagggatat ggctttgtct ccttttcaa 300
caaatgggat gctgaaaacg ccattcaaca gatgggtggc cagtggcttg gtggaagaca 360
aatcagaact aactgggcaa cccgaaagcc tcccgctcca aagagtacat atgagtcaaa 420
taccaaacag ctatcatatg atganggtgt aaatcagtct aatccaagca actgtctgta 480
t 481